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THE SOLUTION OF CERTAIN FUNDAMENTAL IMMUNOLOGICAL PROBLEMS BY STUDIES ON Rh SENSITIZATION

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IN a previous report²² is described the discovery of two forms of Rh antibodies, namely, bivalent (or agglutinating) Rh antibodies and univalent (or blocking) Rh antibodies, as well as the implications of these observations for other antigen-antibody systems and in allergic diseases. During the four years which have followed, these observations have been confirmed and extended.

For performing serological tests red cells have many advantages. They form stable suspensions, and the individual cells are large and can be seen under the low power of a microscope. Blood is easy to procure and easy to work with, both in immunization experiments and in *in vitro* tests. Blood obtained from healthy human beings and animals is noninfectious as well as nontoxic. Because of the relatively small surface in relation to volume in comparison to soluble antigens or bacteria, relatively low titers of specific antibodies are sufficient to bring about distinct clumping. Thus, red cells are readily available, stable, specific, and sensitive antigens.

There is no reason to believe that the immunologic principles applying to other antigen-antibody systems involving, for example, bacteria or soluble proteins are essentially different from those which apply to blood cells. Therefore, studies on the serological behavior of blood cells constitute an ideal approach to the solution of controversial immunological questions. Considerable impetus was given to the study of the serological reactions of the red cells by the discovery of the rhesus factor and the resulting

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increased interest in blood group reactions. In this presentation I propose to discuss several immunological questions of interest to the allergist in the light of more recent investigations on blood group factors, especially the rhesus factors.

UNITARIAN HYPOTHESIS; UNIVALENT AND BIVALENT ANTIBODIES

Hardly anybody mentions the unitarian hypothesis any longer, although until relatively recently this concept was accepted by a large body of workers in the field of immunology. While it was readily appreciated that a complex antigen like a red cell (and, in fact, based on the pioneering investigations of Landsteiner, even a simple chemical compound) can elicit the formation of antibodies of more than one specificity, there used to be a difference of opinion whether antibodies of a single specificity could have more than one molecular form. According to the unitarian hypothesis, the various *in vitro* phenomena, agglutination (or flocculation), precipitation, lysis, complement fixation, and opsonic action were considered to be manifestations of the activity of a single form of antibody modified by the special conditions of the experiment. Today, largely as a result of studies on Rh antibodies, it is generally agreed that antibodies of identical specificity may exist in several molecular forms, of which only two principal forms, namely, the so-called univalent and bivalent antibodies, need be taken into account for practical purposes.

The first tests for Rh antibodies in human sera were carried out by the classic agglutination method in saline media. The existence of individuals with severe manifestations of Rh sensitization whose sera contained no demonstrable Rh agglutinins, caused me to suspect the existence of another form of Rh antibodies capable of combining with Rh-positive cells in saline media but without clumping them. In fact, such antibodies could be demonstrated with the aid of the blocking test.²⁰ (Later more sensitive methods of demonstrating these antibodies were devised, namely, the conglutination²¹ and the antiglobulin⁵ tests, and the use of test cells treated with proteolytic enzymes.¹² In order to visualize better the difference in behavior of the two forms of Rh antibodies, one may postulate that Rh agglutinins are bivalent (or multivalent), while Rh blocking antibodies are univalent (Fig. 1).^{20,21} Naturally, the existence of two major forms of antibodies, "bivalent" and "univalent," could hardly be a phenomenon peculiar to Rh sensitization alone; and, in fact, evidence has accumulated that this principle applies to all antigen-antibody systems.

Thus, there is no longer any doubt that the unitarian hypothesis is incorrect. While in saline media bivalent Rh antibodies clump red cells containing the corresponding agglutinin, univalent Rh antibodies "coat" or "block" Rh-positive cells without clumping them. Antigens sensitized by their specific univalent antibodies may fix complement, and in favorable instances red cells (or bacteria) coated with their specific univalent anti-

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body may undergo lysis, in the presence of complement, or phagocytosis. Witebsky et al⁴² further demonstrated the existence of two forms of Rh antibody by their separation *in vitro* from the same antiserum by dialysis. *In vivo*, the two forms of antibody are separated by passage through the

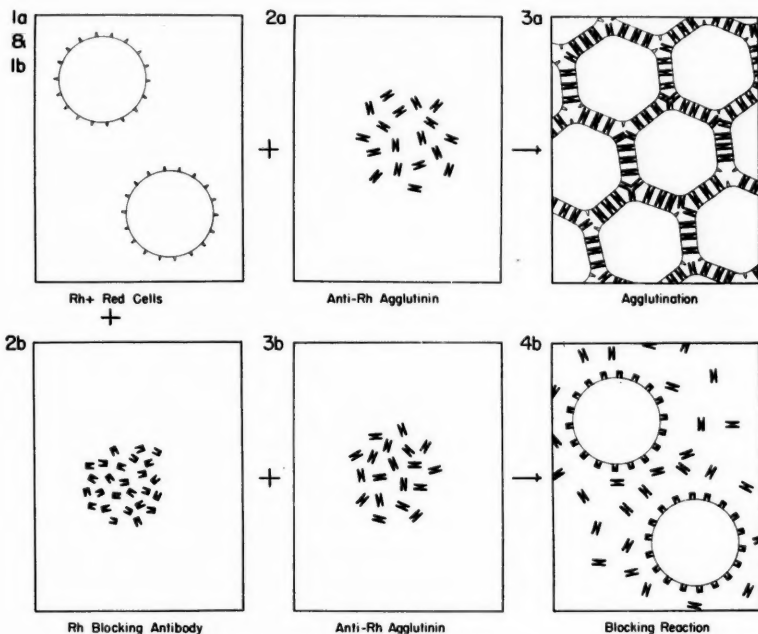


Fig. 1. Comparison of Rh Agglutination and Blocking Reaction.
(Test in Saline Media)

placenta, presumably because of the difference in their molecular size; the univalent antibody passes readily into the fetal circulation, while the bivalent antibody is held back by the intact placental barrier.²²

Of greatest interest to allergists is the evidence indicating that while univalent antibodies are responsible for one's immunity to pathogenic microorganisms, bivalent antibodies appear to be the basis for the various allergic phenomena—hay fever, asthma, and eczema—which have made the specialty of allergy necessary. On the other hand, while univalent antibacterial and antitoxic antibodies by their ability to traverse the placental barrier are largely responsible for a baby's neonatal immunity, it is the univalent Rh (or other blood type specific) antibody which causes erythroblastosis fetalis, because bivalent antibodies do not pass the intact placental barrier and therefore can be exonerated.

The differences between univalent and bivalent antibodies are sum-

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TABLE I.
DIFFERENCES BETWEEN "UNIVALENT" AND "BIVALENT" ANTIBODIES

Characteristics	Bivalent Antibodies	Univalent Antibodies
Common names	Agglutinin, precipitin	Glutinin, blocking antibody
Usual time of appearance in the course of immunization	Early	Late
Resistance to heating	Relatively thermolabile	Relatively thermostabile
Reaction with cells in saline media	Clumps cells by agglutination	Usually coats cells without clumping them
Reaction with cells in plasma, serum and other colloid media	Clumps cells by agglutination	Clumps cells by conglutination
Nature of clumps	Easily dislodged from glass surface	Tend to adhere to glass surface
Specificity of clumps	Specific—clumps contain only one type of cell	Nonspecific—clumps may contain more than one type of cell
Reaction with cells in presence of complement	Does not fix complement or lyse cells	Fixes complement and lyses cells
Opsonic action	None	Positive, in presence of complement
Chemical nature	"Euglobulin": precipitated by sodium sulphate solutions of concentrations 13.5 to 17.4 per cent	"Pseudoglobulin": precipitated by sodium sulphate solutions of concentrations 17.4 to 21.5 per cent
Electrophoretic behavior	Alpha and beta globulins	Gamma globulins
Sedimentation constant	17	7
Probable molecular weight	930,000	155,000
Diffusibility	Poor	Good
Behavior relative to placenta	Held back by the intact placenta	Passes through placenta readily
Half-life	Not yet determined	30 to 35 days
Role in erythroblastosis	Not significant	Major
Role in immunity	Precipitating antibody	Protective antibody; antitoxin
Role in allergy	Sensitizing antibody (reagin)	Blocking antibody

marized in Table I. Some confusion has resulted from the fact that most of the studies on these two forms of antibodies have been carried out on Rh antibodies. For example, many workers have incorrectly assumed that regardless of specificity, antibodies for red cells which are univalent will always coat the cells in saline media and block the antigenic sites without clumping the cells, and that if clumping occurs in saline media the antibodies in question must be bivalent. This is not true, because the nature of the agglutinin (or antigen) also influences the reactions obtained.⁴¹ The agglutinogens of each blood group system appear to be repeated more or less regularly about the periphery of the discoplasma, there being separate sites for agglutinogens from systems A-B-O, M-N-S, Rh-Hr, et cetera (Fig. 2).²⁴ An important characteristic influencing the behavior of blood group antibodies appears to be the number of sites for the corresponding specific agglutinin on the periphery of the red cells; in fact, that is probably the chief reason why, for example, anti-A and anti-B antibodies behave differently from Rh-Hr antibodies. Evidence has been adduced to show that there are many more sites per red cell for A-B-O agglutinogens than for Rh-Hr agglutinogens.² This may explain why specific hemolysis by A and B antibodies plus complement is readily demonstrable *in vitro*, while hemolysis does not occur in tests with Rh and Hr antibodies. On the other hand, while univalent Rh₀ antibodies of high enough titer can completely "block" Rh-positive cells and render them inagglutinable by Rh₀ bivalent antisera, blocking of A and B agglutinogens has never been convincingly demonstrated *in vitro*, presumably because the number of antigenic sites is too high. The combination between antigen and antibody is reversible, and when antibodies separate from the

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red cell surface there is competition between free univalent and bivalent antibodies for the available antigenic sites. When the number of specific sites per cell is small, and univalent antibody is present in the antiserum in sufficient excess, the likelihood is small that sufficient bivalent antibody

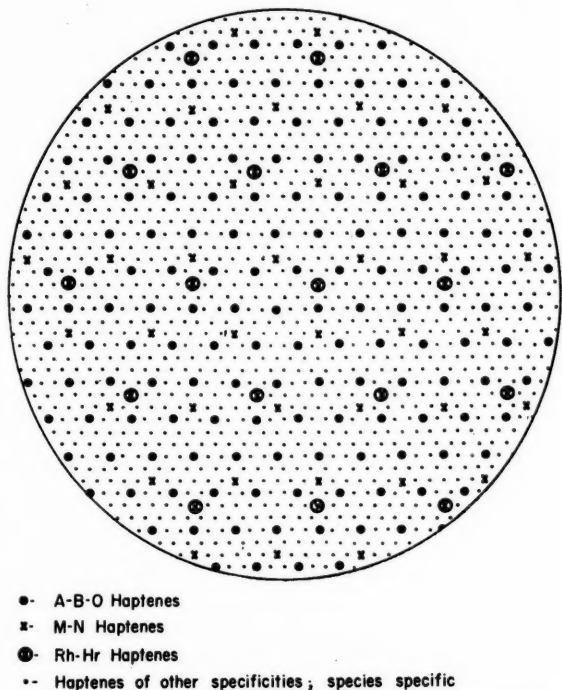


Fig. 2. Diagrammatic Representation of the Hypothetical Arrangement of Agglutinogens About the Periphery of the Human Erythrocyte.

will become adsorbed to link the cells together. On the other hand, when the number of specific sites is high, complete blocking is hardly possible. Thus, blocking as a method of recognizing univalent antibodies is not applicable to the A-B-O system.

It is fortunate that studies on Rh sensitization have suggested a method of differentiating univalent and bivalent antibodies of any specificity for antigens of every kind. This depends on the observation^{22,36} already mentioned that univalent Rh antibodies readily traverse the intact placental barrier, while bivalent Rh antibodies do not. If one assumes that all placenta-passing antibodies correspond to the "univalent" form, one finds, for example, that complement-fixing antibodies such as those responsible for the positive Wassermann test,^{22,16} hemolysins and bacteriolysins, and

antitoxic immune antibodies are univalent; whereas the reagents responsible for hay fever and asthma do not pass the placental barrier and therefore are presumably bivalent.¹⁷

MECHANISM OF RED CELL CLUMPING;* "CONGLUTININ"

Normal red cells suspended in saline solution are prevented from clumping together by the negative net charge on their surface. When this surface charge is reduced below a certain critical potential, as when the cells are suspended in isotonic glucose, agglomeration occurs, which is readily reversible by transferring the cells to saline media. When specific bivalent antibodies combine with red cells suspended in saline solution, the cells are agglutinated because the antibodies link the cells together, thus overcoming the repulsive force produced by the negative surface charge. On the other hand, univalent Rh antibodies cannot link saline suspended Rh-positive cells together; when they coat red cells in saline media there is a reduction of the surface charge but not below the critical potential, so that clumping does not occur. In colloid media, colloids adsorbed onto the surface of the red cells apparently reduce the negative surface charge, and when such Rh-positive cells combine with univalent antibodies the charge is further reduced below the critical potential, so that the cells stick together (conglutination). Furthermore, treatment of red cells by proteolytic enzymes reduces the surface charge, as shown by the reduction of their rate of migration in an electric field,¹⁴ so that when such enzyme-treated Rh-positive cells combine with univalent Rh antibodies, the further reduction in surface charge brings this well below the critical potential, and strong clumping results.³¹

In the case of the A-B-O system, the number of antigenic sites per red cell is presumably so high that mere coating of the untreated cells suspended in saline solution by specific A and B univalent antibodies may bring the surface charge below the critical potential, and clumping by conglutination may then result even in the absence of conglutinin, or in the presence of only small amounts. However, suspension of the red cells in plasma or acacia will increase the intensity and titers of the reactions obtained. Thus, the difference between agglutination and conglutination which helps distinguish univalent and bivalent Rh antibodies is not readily applicable to the A-B-O system. Moreover, in the case of antibodies for soluble antigens such as egg albumin or serum proteins, there is no simple *in vitro* method of distinguishing univalent and bivalent antibodies.

Univalent and bivalent antibodies can often be differentiated with the aid of mixed agglutination systems for morphologically distinguishable antigens, such as red cells and bacteria.²⁹ To perform such tests, the two antigens, red cells and bacteria, are pooled; and the two corresponding antisera are also pooled. The pooled serum is tested against the pooled antigens, and the clumps resulting are examined micro-

*The description given here of the difference between agglutination and conglutination is more detailed and differs in certain respects from that offered previously.

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scopically. If the original antisera both contain bivalent antibodies, the clumps formed are largely specific, that is, each clump contains only one kind of cell, erythrocytes or bacteria; on the other hand, if the original antisera both contain univalent antibodies, the majority of clumps contain a mixture of cells.⁹

When describing the Rh conglutination reaction, this writer originally postulated²¹ the existence in plasma of a colloidal complex of serum albumin and globulin, designated as conglutinin, which was adsorbed by the coated Rh-positive cells and caused them to stick together. The observation that strong solutions of pure albumin or globulin have lower conglutinating activity than weaker solutions of mixtures of albumin and globulin in optimal proportions seemed to support that hypothesis.³⁰ However, it was not possible to confirm the supposed formation of complexes when the mixtures of albumin and globulin were subjected to electrophoretic analysis.²⁷ The simpler explanation presented here obviates the need to postulate the existence of a special substance, conglutinin. Presumably when red cells are suspended in albumin solutions, albumin is adsorbed onto the surface of the cells; similarly, cells suspended in globulin solutions adsorb globulin, whereas when cells are suspended in plasma or serum, both serum globulin and serum albumin are adsorbed (cf. Ponder¹³). If, as seems likely, albumin and globulin are adsorbed onto different portions of the discoplasma, the reduction in surface charge would be greater when cells are suspended in plasma than in pure albumin or globulin, thus explaining the greater conglutinating action of the former. Similarly, the low conglutinating activity of cord serum may be due to the relatively low concentration of proteins in it, while the rise in activity immediately after birth may possibly be attributed to dehydration and resulting hemoconcentration. This, perhaps, may be the main reason why the first few days after birth are so critical for the erythroblastotic baby.

Another important protein adsorbed onto the red cell surface from plasma is fibrinogen. When the fibrinogen content of the plasma is considerably elevated, as in pregnancy and pneumonia, the relatively large quantities of fibrinogen on the red cell surface cause the cells to undergo rouleaux-formation, presumably because of the regular orientation of the elongated fibrinogen molecules. In *in vitro* tests rouleaux-formation has been mistaken for agglutination, and thus has been a source of errors in grouping and cross-matching tests. Fibrinogen and other normal plasma proteins are readily removed from the red cell surface by washing the cells with saline solution. On the other hand, specific antibody globulin such as univalent Rh antibodies is firmly bound by Rh-positive cells, so that they are not removed by ordinary washing with saline solution. This, in fact, is the basis for the antiglobulin (Moreschi-Coombs) test for coating of red cells by Rh antibodies, autoantibodies, and other antibodies.

The red cell surface has the capacity to adsorb many other substances. For example, the ability of red cells to adsorb viruses is the basis of the Hirst agglutination phenomenon and a relatively simple *in vitro* test for influenza antibodies. The rather firm adsorption of tuberculo-protein by red cells is made use of in a sensitive test for antibodies for tubercle bacilli (Middlebrook). Based on these observations, the following hypothesis is offered for the function of red cell agglutinogens, of which such a large variety dot the periphery of the red cells, repeating themselves

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at regular intervals so as to give the discoplasma a mosaic structure. It is postulated that the circulating red cells adsorb onto their surface viruses, toxins, and other foreign substances which are not removed by the leukocytes from the blood stream, and thus render them innocuous, each agglutininogen presumably having the ability to adsorb different chemical substances.

ANTIBODY FORMATION; PERSISTENCE OF IMMUNITY

When one endeavors to produce Rh antibodies by deliberately injecting Rh-positive blood into Rh-negative male volunteers, one finds that a minimum of two injections is required. The first injection appears to act in most instances as a "primer," and then after a suitable latent period (usually at least three or four months in duration), a second injection often elicits the appearance of Rh antibodies within five to ten days. Individuals vary in their response, so that only 40 per cent become isosensitized after two injections, but the percentage increases with the number of injections to more than 80 per cent after six properly spaced injections.^{23,37} The failure of some individuals to respond may perhaps be attributed to the presence in their red cells of a variant of the Rh factor not demonstrable by present-day methods. At any rate, nothing is accomplished by increasing the dose or frequency of the injections, since the latent or preparatory period seems to be an essential part of the process of immunization. Thus, ten transfusions each of 500 cc of Rh-positive blood within a fortnight would be less likely to sensitize an Rh-negative individual than two injections of only 2 cc each, spaced four months apart.

While the type as well as the titer and avidity of the antibodies varies with the individual immunized, the course of antibody formation tends to follow a uniform pattern. The antibodies which first appear are often of the bivalent variety, but these generally disappear after a short time and are replaced by univalent antibodies. Actually, there is evidence that in most cases the production of bivalent antibodies continues but that the presence of these antibodies is not readily demonstrable because they are prevented from acting by the more potent univalent antibodies present in the same serum.⁴⁰ Exceptional individuals will produce excessive amounts of bivalent antibodies, and perhaps it is such individuals who under favorable conditions of exposure would be more likely to develop allergic disease. As has been shown in previous papers,⁴³ the predisposition to allergic diseases (and, therefore, probably also the capacity to form bivalent antibodies in general) has a constitutional hereditary basis.

Similarly, in primary syphilis the first tests to become positive are generally the precipitation and flocculation tests, probably because these reactions are produced by bivalent antibodies. Later on, of course, the complement fixation tests become positive, after univalent syphilitic reagin has been formed. It is of interest, moreover, that even in the earliest studies on serum disease, the difference in time of appearance of sensitizing and immune antibodies was observed, though at that time the distinction between bivalent and univalent antibodies was not appreciated. As an

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TABLE II. DEVELOPMENT OF TOLERANCE TO INJECTIONS OF HORSE SERUM
Patient repeatedly injected with diphtheria antitoxin because of malignant diphtheria

Injection Number	Date (1903)	Time Interval Days	Reaction and Remarks
1st	Feb. 7	0	18 cc of serum given. Six days later universal urticaria (due to serum disease).
2nd	Feb. 18	11	4 cc afternoon of injection, arm slightly edematous
3rd	Feb. 21	14	4 cc arm slightly edematous
4th	Feb. 24	17	4 cc arm slightly edematous
5th	Feb. 27	20	4 cc after half hour area of injection red, 24 hours later, slightly swollen.
6th	Mar. 2	23	3 cc soon followed by slight swelling at local site; at 24 hours no reaction.
7th	Mar. 5	26	3 cc no reaction
8th	Mar. 8	29	3 cc no reaction
9th	Mar. 16	37	3 cc no reaction

From V. Pirquet and B. Schick: *Serum Sickness* (Engl. transl.). Baltimore: Williams & Williams, pp. 111-112, 1951.

example, the case shown in Table II is cited, taken from the book of von Pirquet and Schick on "Serum Sickness."¹⁹ This young patient was given 18 cc of horse serum (containing diphtheria antitoxin) subcutaneously in treatment of malignant diphtheria and thereafter was given eight additional subcutaneous injections of 4 or 5 cc each over a period of thirty-seven days. Six days after the first large injection the patient developed a generalized urticarial eruption; the second to sixth injection caused only relatively prompt local reactions of decreasing intensity, while the seventh to ninth injections caused no reaction at all (Table II). The latent period after the first injection before symptoms appeared was of course due to the initial absence of antibodies, which were formed after six days. The generalized eruption was then due to the simultaneous presence in the body of horse serum and specific bivalent antibodies for horse serum, and this subsided when the horse serum proteins were eliminated from the body. The prompt local reactions were due to the introduction of fresh horse serum into an individual with circulating bivalent antibodies for horse serum. The local reactions diminished in intensity and finally disappeared, presumably because the bivalent antibodies disappeared or diminished in titer and were replaced by univalent antibodies.

It is not possible to desensitize a sensitized Rh-negative individual by injections of Rh-positive blood. If such an individual survives a large transfusion of Rh-positive blood, there is a temporary drop in titer (negative phase) due to absorption of antibodies, followed by a rise in titer to a level usually higher than that before the transfusion (unless the titer has already reached its maximum). As already mentioned, however, if the injections are repeated, not only does the titer tend to rise but the quality of the antibodies changes as univalent antibodies replace bivalent* antibodies originally present. This, in fact, is the principle used when treating hay fever and poison ivy dermatitis, by injecting progressively increasing

*Building up tolerance for large doses appears to be important though not absolutely essential for successful treatment. The reason for this may be that small doses generally elicit the formation of bivalent antibodies, whereas larger doses are more likely to induce the production of univalent antibodies.

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doses of the offending antigen.* The body is caused to form high-titered specific blocking (univalent) antibodies, so that when the individual is exposed to the antigen later on, the blocking antibodies combine with the antigen and thus prevent the reagins (bivalent) antibodies from doing so. Inasmuch as allergic manifestations generally accompany the *in vivo* combination of antigen with bivalent antibody, and not with univalent antibodies, allergic individuals treated in this way are usually benefited. On the other hand, injections of Rh-positive blood into expectant sensitized Rh-negative mothers would tend to aggravate the situation by increasing the titer of univalent Rh antibodies, because it is the univalent and not the bivalent antibodies which pass into the baby *in utero* and combine with his blood cells to produce disease.

When an Rh-negative individual who has been sensitized to the Rh factor receives no additional parenteral inoculation of Rh-positive blood, the Rh antibodies present in the serum persist for an indefinite period of time.^{18,33} The bivalent Rh antibodies usually disappear within a relatively short time, but the univalent antibodies remain and decline in titer only gradually over the years. In fact, we succeeded in demonstrating the presence of univalent Rh antibodies in one Rh-negative woman who had had no pregnancy nor blood injection that might have resensitized her for more than twenty years. These findings agree with the observation that after recovery from many infectious diseases the immunity acquired may persist for the remainder of one's life (cf. Burnet and Fenner³). While this is an advantage for immunity, at the same time this phenomenon prevents strongly sensitized Rh-negative women from having normal Rh-positive babies. Moreover, this should be borne in mind when confronted with so-called Wassermann-fast patients; such individuals should not be treated on the basis of the blood tests alone, because many such individuals have already recovered from the infection and are merely good antibody producers with a high titer of residual univalent syphilitic antibodies. Similarly, in the case of allergic individuals, if all contact with the offending antigen is avoided, the reagins tend to disappear while the blocking antibodies persist.

ANAMNESTIC REACTION

The term *anamnetic reaction* has been used in several ways, of which only one concept is valid: namely, as applied to describe the accelerated and exaggerated immune reaction which follows the reinjection of the specific antigen after a long interval of time. For example, when a sensitized Rh-negative person who has not been exposed to Rh antigen for many years is given an intravenous injection of 1 cc or even less of Rh-positive blood, within five to ten days the antibody titer will rise to a high level even though the antibodies may have been hardly demonstrable before the injection. If the injections are properly spaced, bivalent Rh antibodies may reappear along with univalent Rh antibodies, but the former

*See footnote on preceding page.

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soon disappear while the latter persist. In one unusual Rh-negative individual who was given small injections of Rh-positive blood at two-year intervals, the titer of the bivalent antibodies attained the extraordinary level of 7500 units, the highest titer ever encountered by us.[†] These bivalent antibodies gradually declined in titer over a period of months, and then univalent antibodies of approximately 250 units became demonstrable. Actually these univalent antibodies had been present all along, because when serum obtained at the peak of the immunization was heated at 60° C for one hour, the thermolabile Rh agglutinins were destroyed, disclosing the presence of the weaker univalent Rh antibodies.²⁸

These observations fit with the observation that allergic individuals are generally most severely affected by antigens with which contact occurs at wide intervals, namely, pollens, seasonal foods like nuts and strawberries, stings by bees and other insects, and the like. Ratner¹⁵ and others have emphasized how the relief bottle sometimes given to nursing newborn babies may prime the baby and thus give rise to allergic disorders later on when the baby is weaned. In the interval between exposures the reagins tend to disappear, but on re-exposure they presumably rapidly reappear in high titer (anamnestic reaction) and cause allergic manifestations. This, of course, is also the explanation for the accelerated serum disease which follows reinjection. If continuous contact with the allergen is maintained, as in the perennial treatment of hay fever, or daily ingestion of a food, the reagins decline in titer while potent blocking antibodies are formed, so that immunity replaces hypersensitiveness.

The term *anamnestic reaction* has also been used to imply that an accelerated immunological response may result from exposure to unrelated antigens, or follow injections of materials other than the specific antigen. This erroneous idea is apparently based on two factors: (1) the supposedly unrelated substance may actually be related to the specific antigen and the cross-reacting antibody mistaken for the specific antibody; (2) more commonly, errors occur in antibody titrations. It is not generally appreciated that antibody titrations even when carefully carried out by experts have an experimental error of at least one dilution (100 per cent). Since titrations are generally carried out with progressively doubled dilutions, a difference between 64 and 128 units has no greater significance than between 1 and 2 units. The use of algebraic instead of geometric scales when graphing titers makes the difference between 64 and 128 units appear as significant as between 0 and 64 units, and thereby has misled some workers, when interpreting the results of titrations. Recently, for example, a great number of reports have appeared claiming a nonspecific anamnestic response when sensitized Rh negative women carry Rh-negative fetuses.

[†]Antibodies have mass, and so their titer cannot exceed certain maximum values. Reports in the literature of titers reaching the millions are due to faulty technique, and a titer of 82 million units, for example, as claimed by one author, would imply the presence of 60 grams of antibody protein per cc of serum!

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If this were true then it should be likewise possible to prepare anti-Rh sera or increase Rh antibody titers by injections of Rh-negative blood; but no one would subscribe to such an idea. In a series of eighteen such cases studies by Wiener et al³² not once was there a rise in Rh antibody titer either during the pregnancy or after the birth of the Rh-negative child. Accordingly, the incorrect expression *nonspecific anamnestic reaction* is based on faulty observations and should be discarded, and the term *anamnestic reaction* should be used only to describe the accelerated and exaggerated response which follows reexposure to the *specific* antigen.

TABLE III. COMPARISON OF REAGINS IN A MOTHER AND HER NEWBORN CHILD

Serum of	Titer of Reagins by		
	Kline Flocculation Test		Kolmer Wassermann Test
	Diagnostic	Exclusion	
Mother	80	128	36
Baby (cord serum)	6	7	32

ANTIBODIES AND GAMMA GLOBULINS IN THE NEWBORN; HALF-LIFE OF UNIVALENT ANTIBODIES

As attested by a large literature, newborn infants are relatively incapable of producing antibodies, and depend for their immunity largely on antibodies passively acquired from the mother. In animals such as sheep, cattle, and dogs, antibodies are not present at birth but appear in the serum after ingestion of colostrum (for literature see Burnet and Fenner³). The importance of colostrum in these animals has been demonstrated by the observation that calves prevented from nursing usually die shortly after birth from *B. coli* septicemia. In man, the antibodies are passively acquired by the fetus by placental transfer from the mother while *in utero*; the additional amounts imbibed in the colostrum are relatively insignificant, as shown by the observation that artificially fed infants thrive as well as breast-fed ones.

Further light has been thrown on this subject by studies on Rh and other blood group antibodies in the newborn. At birth, the Rh-negative baby of a sensitized Rh-negative mother generally has the identical titer of univalent Rh antibodies as its mother, as shown by our own study of more than twenty such cases. When the maternal serum contains bivalent Rh antibodies (Rh agglutinins), on the other hand, these antibodies are not demonstrable in the baby's serum.^{22,36} Thus, univalent Rh antibodies readily traverse the placental barrier and pass into the fetal circulation until the titers of the antibodies on both sides of the placenta become equal; bivalent Rh antibodies, on the other hand, are held back by the intact placenta. Since the same principle applies also to antibodies of other specificities, almost invariably the baby at birth is immune but not

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allergic, the scope of its immunity depending on the antibodies passively acquired from the mother. This serves to underline the uselessness of umbilical cord Wassermann tests still being done in some hospitals; such tests merely determine indirectly the maternal syphilitic reagins, but not

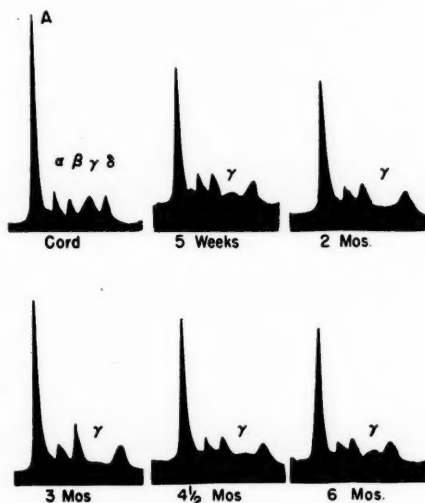


Fig. 3. Serum Gamma Globulin in Babies.

the baby's, because the baby's own antibodies are generally not produced until later on. As shown in Table 3, for example, the titers of such antibodies in maternal and cord blood are equal by the complement fixation technique, which detects univalent antibodies, but not by the flocculation technique.

The presence of Rh antibodies in Rh-negative babies of sensitized Rh negative mothers provided an ideal opportunity to determine the half-life of such univalent antibodies in man. The passively acquired Rh antibodies are gradually eliminated from the baby's body, and if one allows also for the dilution effect produced by the baby's growth; one finds the half-life to be approximately thirty-five days. Applying the same calculations to observations on passively acquired diphtheria bacterial antibodies and antitoxins, one obtains, as expected, the same half-life of thirty-five days. In the *actively* immunized mother, on the other hand, the antibody titer shows hardly any change for months or years, indicating that in such actively immunized individuals the univalent antibodies are being regenerated continuously, at a rate almost equal to the rate of destruction. Unfortunately, no valid method has yet been devised for determining the half-life of bivalent antibodies (reagins). The rate of elimination of passively acquired Rh antibodies has been compared in breast fed and artificially fed

Rh-negative babies. Since no significant difference was found, this indicates that little if any Rh antibody is absorbed by the ingestion of milk of sensitized mothers. This supports the view that there is no contraindication to breast feeding for erythroblastotic babies.

Since immune antibodies appear to be gamma globulins, these results suggested the study of gamma globulins in newborn infants. As shown in Figure 3, the gamma globulin peak in newborn babies is about the same as in the mother; it gradually declines as the baby grows older to reach a minimum at three to four months of age and then gradually rises again. While this indicates that most of the gamma globulin of the newborn has been passively derived from the mother, the fact that the gamma globulin peak does not decline as rapidly as the titer of the passively acquired antibodies suggests that even shortly after birth the infant is already beginning to produce some of its own gamma globulin.

The relative inability of newborn babies to form antibodies is well illustrated by our experience when transfusing erythroblastic babies. On the basis of antenatal tests we are able, as a rule, to determine before birth which babies are likely to require treatment and keep on call type rh donors of the mother's blood group.^{38,39} For example, when the mother belongs to group A, we use a group A donor even though the baby later proves to belong to group O. In contrast to the situation in older children and adults, such group O babies tolerate well transfusions of group A blood, which survives in their circulation for about 100 days just like compatible blood of the baby's own group, and after the group A blood has disappeared, there is no unusual production of immune A isoantibodies.²²

Recently we encountered an unique exception to the rule that newborn infants do not produce antibodies.⁴² The infant in question was born with jaundice, anemia, and erythroblastemia; had a massively enlarged liver and spleen; exhibited hemorrhagic phenomena; had a positive direct anti-globulin test; and was diagnosed as erythroblastotic. However, mother and baby were both group B Rh positive, and no abnormal antibodies were demonstrable in the mother's serum. On the other hand, the baby's serum contained bivalent cold autoagglutinins of high titer (more than 1,000 units), which he had apparently formed *in utero*, thus accounting for the syndrome which he exhibited at birth. Similar precocious formation of bivalent antibodies for allergens at birth or even *in utero* may account for those rare instances of infantile eczema which begin shortly after birth.

As already pointed out, the baby when born is generally passively immunized but not allergic. Gradually the passively acquired antibodies are eliminated (half-life, thirty-five days) and the baby begins to form his own antibodies. Since the actively produced antibodies are commonly bivalent at first, and not until later on are they replaced by univalent antibodies, there is a short period during which the infant is prone to

RH SENSITIZATION—WIENER

allergic disorders caused by allergens in foods, inhalants, and microorganisms. Presumably, in most babies allergic manifestations do not appear because blocking antibodies passively acquired from the mother tide the babies over until they form their own univalent antibodies. In babies who develop eczema, most likely specific blocking antibodies were either lacking from the mother's serum or the babies were constitutionally predisposed to produce excessive titers of reagins (bivalent antibodies).⁴³ In any event, these considerations would explain the usual time of onset of infantile eczema at two to three months of age and the spontaneous recovery which generally takes place at the age of two years, by which time the baby has, as a rule, formed adequate amounts of immune (blocking) antibodies. The logical treatment of infantile eczema is to immunize* the affected babies; to avoid contact with the offending allergen is sometimes necessary but merely delays the solution of the problem. It may be worth while in selected cases to try injections of immune globulin, which theoretically could tide the baby over until such time as he develops his own immune (or blocking) antibodies. In fact, treatment of two babies with intractable eczema by repeated intramuscular injections of human gamma globulin caused the skin eruption to clear up.⁴⁰

When determining the offending allergens in allergic disorders of infants, one usually resorts to passive transfer tests. Obviously, the results of the tests depend on the subject used as well as the reagins in the baby's serum, because if the subject selected possesses strong immune (blocking) antibodies for the allergen in question, false negative reactions might result. One must bear in mind also that the baby's serum generally contains some blocking antibodies as well as reagins. However, the baby's blocking antibodies rapidly diffuse (Table I) from the skin site, while the larger reagin molecules remain behind to react with the allergen when it is applied twenty-four hours later.† Thus, the difference in diffusibility is the basis for a second *in vivo* method of separating univalent and bivalent antibodies. By this method one can isolate reagins (bivalent antibodies) free of blocking (bivalent) antibodies, while placental transfer yields univalent antibodies free of bivalent antibodies. *In vitro*, the antibodies can be separated by making use of the difference in their heat stability,²⁸ or the readiness with which they precipitate out upon dialysis against distilled water.⁴⁴

AUTOANTIBODIES AND DISEASE

By leading to new methods of detecting antibodies, studies on the Rh

*Persistence with oral administration often does not constitute adequate immunization, because of the small quantities of allergen absorbed (cf. footnote to page 12). If parenteral immunization such as is used in hay fever is impracticable or unsuccessful, it may be necessary to withdraw the allergen temporarily until the reagins have diminished in titer. In many cases, upon readministration of the allergen the body then responds by producing blocking antibodies instead of reagins.

†This explanation is different from the one usually offered, which postulates that during the twenty-four-hour interval the reagins are fixed to the tissues.

RH SENSITIZATION—WIENER

factor have been indirectly responsible for the revival of interest in diseases caused by autoantibodies. According to the principle of "horror auto-toxicus," enunciated by Ehrlich, antibodies are never produced which are capable of reacting with constituents of the body proper. While this principle is valid in general, there are circumstances under which it does not hold, and the production of autoantibodies for red cells, for example, can give rise to a hemolytic anemia comparable in many respects to erythroblastosis fetalis caused by Rh antibodies.

The relative inability of the body to form antibodies against its own constituents is now ascribed to the phenomenon of "immunologic paralysis."⁸ For antibody formation to occur, the antigen must reach the antibody-forming cells in doses falling within a certain optimal range; if excessive amounts of antigen are present, the saturated antibody-forming cells cannot react. For example, according to Felton,⁸ mice injected with excessively large amounts of type specific pneumococcal polysaccharide retain this substance within their bodies for the remainder of their lives, and while such mice lose their ability to form antibodies for pneumococcal polysaccharides of the specific type originally injected, they retain their ability to be immunized against pneumococci of other types. Nevertheless, there are circumstances under which antibodies may be formed against normal body constituents.

First, autoantibodies for red cells may be of heterogenetic immune origin. This statement probably applies, for example, to the natural cold autoagglutinins present in the serum of all normal individuals except during the neonatal period. Shortly after the blood groups were discovered by Karl Landsteiner, he found that when red cells of normal individuals are mixed with plasma (or serum) from the same individual at low temperature, e.g., 5 to 10° C, clumping of the cells usually occurs due to the presence in normal human serum of "cold autoagglutinins." If the tests are carried out using red cells treated with proteolytic enzymes, the clumping is considerably stronger and is observed with virtually all normal human sera except during the neonatal period. The agglutininogen with which the antibody reacts is present in all human blood cells so that the antibody is really a *panagglutinin*; however, the term "cold autoagglutinin" is used to indicate the two most important properties of the antibodies, namely, that they react with the individual's *own* red cells, but only at a *low* temperature. As for the origin of the antibodies, these are believed to be of heteroimmune origin,²⁵ in response to inapparent or manifest infections with microorganisms possessing antigens related structurally to antigens present in human red cells. Thus, these antibodies do not represent a true autoimmunization, and their reactions with human red cells are comparable to the opening of a lock by a skeleton key.

The low avidity of the combination is shown by the fact that normal autoagglutination occurs at low temperature only, because at body tem-

perature thermal agitation prevents and reverses the union of cold autoagglutinins with red cells. For this reason, the cold autoagglutinins apparently have no pathological or physiological importance. However, the titer of the cold agglutinins may be increased in specific infections such as atypical pneumonia, trypanosomiasis, kala-azar, mumps, and infectious mononucleosis, confirming the hypothesis that the natural cold autoagglutinins are of heteroimmune origin. Moreover, when the titer is elevated, clumping may occur also at room temperature and may then interfere with blood grouping and crossmatching tests before transfusions. When the titer is so high that the autoantibodies combine with the red cells also at body temperature, a hemolytic anemia may result. This anemia, as a rule, responds to blood transfusion therapy, and complete recovery generally occurs when the antibody titer falls.³⁵ A particular type of cold autohemolysin is sometimes encountered in individuals with congenital syphilis, in whom it gives rise to the syndrome of paroxysmal hemoglobinuria. A diagnostic test for this disorder was devised by Donath and Landsteiner⁶ as long ago as 1904, which is still in use at the present time.

Second, individuals exist who have a remarkable capacity to form antibodies in general, and such individuals may form true autoantibodies. Examples of individuals with a remarkable capacity to form antibodies are occasionally encountered in blood transfusion practice, where they may pose difficult problems in the selection of compatible donors because of the development of multiple immune isoantibodies. It is significant that such instances of multiple isoimmunization to weak antigens occur far more frequently than would be expected by chance, under the assumption that individuals immunized to one rare agglutinin are no more likely to become immunized to another than a nonimmunized individual selected at random. For example, Callender and Race⁴ encountered a patient with lupus erythematosus diffusus who became immunized in succession to the weak antigens hr' and N , and three additional previously undescribed agglutinogens. Similar cases have been encountered by other investigators. As Wiener²⁶ has pointed out, sera from individuals immunized to poor antigens like hr' and hr'' frequently contain autoantibodies active at body temperature, especially in tests with enzyme-treated red cells. These autoantibodies, in contrast to the cold autoagglutinins, react to about the same titer at body temperature as at refrigeration temperature. Though in some individuals their presence appears to be innocuous, in others they are associated with a chronic hemolytic anemia, subject to exacerbations and remissions, during which the red cells can be shown to be coated with globulin (presumably autoantibodies) by the antiglobulin test. This form of acquired hemolytic anemia, in contrast to that produced by cold autoantibodies, has a protracted course, and despite transfusions, splenectomy, or ACTH therapy frequently terminates with the death of the patient. Based on the newer tests for univalent autoantibodies it has been possible

to establish the connection between certain obscure disease syndromes, just as isoimmunization in pregnancy proved to be the common denominator for congenital hemolytic anemia, icterus gravis neonatorum, hydrops, and certain obscure stillbirths. Thus, under the diagnosis "autoantibody disease" may be included such diverse syndromes as acquired hemolytic anemia, lupus erythematosus diffusus, thrombotic thrombocytopenic purpura, and nonbacterial thrombotic endocarditis.²⁶

Third, it is significant that hemolytic anemia is a not infrequent complication in chronic lymphatic leukemia, lymphosarcoma, and other diseases of the lymphoma group. This is not entirely surprising considering that the present view is that lymphoid tissue, especially plasma cells, is the main source of antibodies.⁷ Recently, the present author studied an elderly male patient with an extensive lymphosarcoma, who had a severe hemolytic anemia. In the serum of this individual cold autoagglutinins of extremely high titer were encountered, thus accounting for the anemia. The antibodies were also present in high concentration in the large volumes of pleural exudate removed by periodically tapping his chest. The anemia failed to respond to splenectomy, ACTH therapy, or multiple transfusion therapy. Significantly, extracts of the tumor removed postmortem showed a high concentration of autoantibodies, in contrast to extracts of other organs, such as kidney.

Finally, attention should be called to the hypothesis that bacteria or viruses, toxins, and other hemolytic agents may alter red cells and thus render them antigenic. The antibodies for such altered red cells, by cross-reacting with normal red cells, are presumed to be capable of giving rise to a hemolytic anemia. A similar theory was invoked a long time ago to explain the reactions of syphilitic reagins with extracts of normal heart muscle, though the preponderance of evidence suggests instead that these antibodies are of heterogenetic origin due to the presence of related lipids in heart muscle and the *treponema pallida*. Recently, the hypothesis has been invoked to explain the so-called collagen diseases, especially rheumatic fever. The hypothesis has derived some support from the experiments of Freund et al¹⁰ and others¹¹ on the experimental production of isoallergic encephalitis by injections of brain tissue rendered antigenic by mixture with dead tubercle bacilli and paraffin.

COMMENT

By discussing the relative rôle of univalent and bivalent antibodies in allergic diseases, it has not been my intention to minimize the important of accessory factors, such as hypoglycemia¹ and the emotional response of the patient. One must never forget that it is necessary to treat not merely the disease but the whole patient as an individual. In erythroblastosis fetalis, while as expected there is a correlation between the titer of the maternal univalent Rh antibodies and the severity of the manifestations in the erythroblastic fetus or infant, exceptional instances exist

RH SENSITIZATION—WIENER

of deaths despite relatively low antibody titers or recoveries despite high titers.³³ This indicates that while the antibodies play the primary rôle in the pathogenesis, in many instances secondary factors may decide the ultimate outcome. Similarly, in allergic disorders one must take into account not only the dosage of offending allergen and the titer of the reagins in the patient's body, but also the fact that there exist individual differences in the constitutional response to the same antigen-antibody combination.

In this presentation, an attempt has been made to describe the average response which occurs following a course of immunization. However the description given here has the serious limitation that it is based largely on experiments with normal Rh-negative male volunteers who were given injections of Rh-positive blood. Allergic individuals, on the other hand constitute a selected group whose immune reactions differ from the norm, and in addition there are wide variations in the response of different individuals, both normal and allergic. Therefore, each problem must be individualized, and when selecting the best treatment course for a patient, one must resort to trial and error to a certain degree. Above all, one must not be overzealous and push the injections in the face of adverse reactions, because this may aggravate the disease or invite a dangerous constitutional reaction.

CONCLUSION

In conclusion, it may be remarked that the concept of two major forms of every specific antibody, univalent and bivalent, has not been fully exploited. Perhaps the reason is that each antigen-antibody system poses somewhat different problems in technique of testing. However, it is believed that the more widespread application of these general principles may possibly lead to a better understanding of the pathogenesis of allergic diseases and to more efficacious methods of treatment. Attention has been called especially to the group of diseases caused by autoimmunization and autosensitization, which offer a challenge and constitute a promising field for future investigations.

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BANTHINE

This is believed to be the first published report of dermatitis due to Banthine. The patient, aged sixty, developed a large duodenal ulcer and was placed on the usual ulcer regimen, including Banthine. Examination after eight days of treatment revealed a generalized papular erythema which quickly developed into acute generalized exfoliative dermatitis. Discontinuance of Banthine resulted in some improvement in the skin condition; resumption of treatment was followed by immediate exacerbation. A subsequent patch test with Banthine elicited a strongly positive reaction.—Clark, R. F. and McNaughton, D. W.: Exfoliative dermatitis due to Banthine. Arch. Dermat. & Syphilol., 66:101, 1952.

HEADACHE STATISTICS: SELECTED DATA

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IN several publications we have reported the various findings of the cross-section headache survey of 4,634 adult individuals.^{1,2,3} It is now possible to coalesce the findings and to emphasize certain of the more important data. It is also possible, in the light of these facts, to form more definite impressions and conclusions. While it is not my intention to review in detail each separate report, certain facts should be restated.

We found that the incidence of all types of headache in the groups surveyed was 64.8 per cent. It was further found that this incidence varied greatly in various segments. Much of these data were tested statistically and seen to be significant.¹ The incidence of headache was found to be inversely proportional to the age in years. In young adult life, between twenty-one and thirty, with its problems and tensions, headache was found in 74.6 per cent. On the other hand, in those over sixty we found headache in only 28.6 per cent. Is this due to a lessening of causative factors in advancing age, or is it due to a lessening of vascular lability dependent on gradual, even though mild, sclerosis of the vessel walls? One may ask, is it due to a lower incidence of extrinsic allergy, or is it due to the fact that the older person is more stable, less volatile, and less influenced by his surroundings? This problem alone calls for further investigation.

Headache was found in 71 per cent of females and 50.7 per cent of males.¹ Women undergo cyclic changes of an endocrine nature. These changes may in themselves act as a nonspecific aggravating factor. Also, as most physicians will agree, women have a different capacity to react to emotional stimuli as compared to men.

The interesting fact was also observed that headache is more common in single persons than in married ones.¹ There is undoubtedly more insecurity and more sexually connected tensions among single people. Even though the single person may indulge in sexual union, such relationships are characteristically unstable and lack the generally deeper emotional stability of marriage. Loneliness itself may cause a feeling of insecurity.

We further see that headache is directly proportional to the degree of education.¹ In college students headache was found in 77.2 per cent, while in those with little or no education the figure was only 38.8 per cent. In freshmen medical students we actually found an incidence of 86.9 per cent.

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HEADACHE STATISTICS—OGDEN

TABLE I
Three Criteria: (a.) Fatigue or being tired; (b.) Emotions; (c.) Worry

Group	I	II	III	IV
Composition of group	(Heterogeneous. Questionnaires answered by individuals)	(Different homogenous segments. Personally interviewed)	(Different homogenous blocks. Well educated. Questionnaires answered by individuals)	Total of groups I, II & III
Number in group	3589	501	544	4634
Number in headache fraction in group	2380	205	420	3005
Number answering affirmatively any one criterion	729	53	146	928
% of headache fraction	30.6	25.9	34.8	30.9
Number answering affirmatively any two criteria	213	20	52	285
% of headache fraction	8.9	9.8	12.4	9.5
Number answering affirmatively all three criteria	46	12	10	68
% of headache fraction	1.9	5.9	2.4	2.3
Total per cent	41.4	41.6	49.6	42.7

We also found that occupation is an important factor.¹ There is more headache among those whose occupations embody more tensions, worry and responsibility. On the other hand, among laborers there was much less headache.

An evaluation of these facts makes it clear that headache depends to a great extent on the type and state of the individual and especially on the particular emotional and occupational situation. In other words, the lability of the vessels is obviously affected by mental influences, which in turn are governed by the individual background.

Can we therefore argue with those who lay great stress on psychogenic factors? Obviously not; however, we may be able to show that other factors such as allergy must be considered.

At this point, the following data may be of some interest. In the questionnaire, we attempted to determine the suspected causes of headache (from the subjective standpoint). Among the various causes listed were three, which may possibly be connected with psychogenic influences. They were (1) fatigue, (2) emotions, (3) worry. The data obtained in the four groups are listed in Table I.

These data and the previously mentioned observations indicate strongly the influence which psychogenic factors play in influencing headache. Likewise we know that "learning to live with one's life situation" may contribute very effectively towards a lack of headaches, as witness the comparatively low incidence of headaches among physicians,¹ who certainly have a good deal of worry and responsibility. It may be that they have acquired the facility of carrying their tensions in such a way that they often avoid inner conflicts, which in others would find expression in the symptom of headache.

It is therefore important never to lose sight of the significance of psychogenic factors. However, just as dangerous an oversight would be to relegate other factors such as allergy, for example, to a minor, irrelevant, or nonexistent role. The background of headache has several component

HEADACHE STATISTICS—OGDEN

parts. It is incomplete when perspective is destroyed by overemphasizing the importance of any one of its parts.

As a consequence, we were also interested in determining the possible

HEADACHE FRACTION

NON-HEADACHE FRACTION

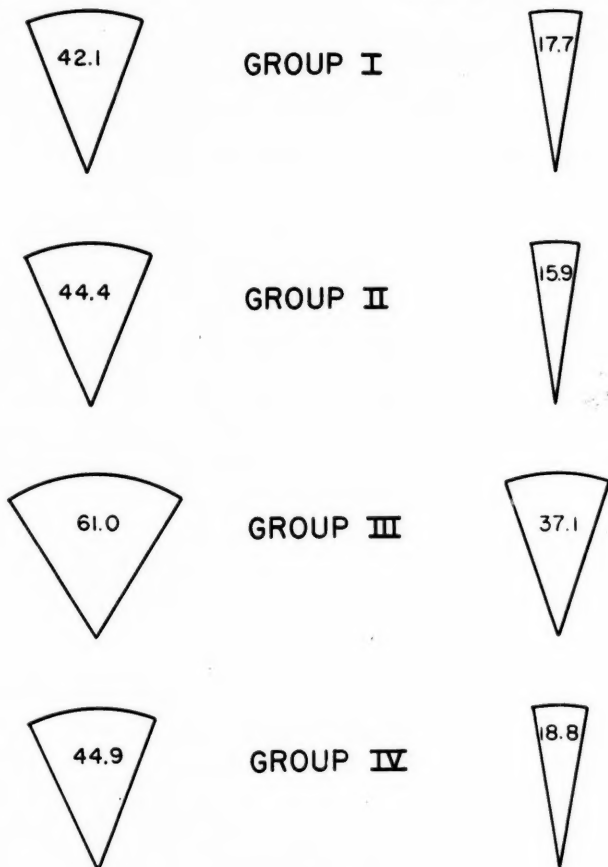


Fig. 1.

relationship of allergy to headache. A statistically significant finding was the fact that in the total nonheadache fraction 81.2 per cent have no nasal symptoms as compared to 55.1 per cent in the headache fraction.¹ Of the nonheadache fraction 86.4 per cent had no chest or throat complaints, compared to 72.1 per cent of the headache fraction. Of the first fraction 23.4 per cent reported "no colds," while only 7.8 per cent of the second made the same report. Urticaria was found in 7.1 per cent of those

HEADACHE STATISTICS—OGDEN

TABLE II

	Group I 3589 Cases*		Group II 501 Cases	
	Nasal symptoms	No nasal symptoms	Nasal symptoms	No nasal symptoms
Segment of group	1187(33.4%)	2372(66.6%)	138(27.5%)	363(72.5%)
Headaches	1003(84.5%)	1377(58.0%)	91(65.9%)	114(31.4%)
No headaches	184(15.5%)	995(42.0%)	47(34.1%)	249(68.6%)
	Group III 544 Cases		Group IV 4634 Cases*	
	Nasal symptoms	No nasal symptoms	Nasal symptoms	No nasal symptoms
Segment of group	302(55.5%)	242(44.5%)	1627(35.3%)	2977(64.7%)
Headaches	256(84.8%)	164(67.8%)	1350(83.0%)	1655(55.6%)
No headaches	46(15.2%)	78(32.2%)	277(17.0%)	1322(44.4%)

*Returns were incomplete in 30 cases in Groups I and IV.

TABLE III

Group	I*	II	III	IV*
No headaches	1179	296	124	1599
No headaches (no nasal symptoms)	995(84.4%)	249(84.1%)	78(62.9%)	1322(82.7%)
No headaches (nasal symptoms present)	184(15.6%)	47(15.9%)	46(37.1%)	277(17.3%)
Hay fever	73(39.7%)	22(46.8%)	16(34.8%)	111(40.1%)
Running nose	38(20.7%)	17(36.2%)	7(15.2%)	62(22.4%)
Sneezing spells	61(33.2%)	22(46.8%)	10(21.7%)	93(33.6%)
Itching nose or eyes	43(23.4%)	13(27.7%)	10(21.7%)	66(23.8%)
Nasal discharge	27(14.7%)	15(31.9%)	7(15.2%)	49(17.7%)
Eye discharge	19(10.3%)	10(21.3%)	4(8.7%)	33(11.9%)
Blocked nose	32(17.4%)	15(31.9%)	15(32.6%)	62(22.4%)
Drip back of throat	51(27.7%)	11(23.4%)	19(41.3%)	81(29.2%)
Sinus trouble	34(18.5%)	15(31.9%)	10(21.7%)	59(21.3%)

with headache, while it was present in only 3.7 per cent of those with no headache. However, this latter finding was not significant because of the small percentages involved. A significant finding was the fact that there is a familial history of allergy in 25.1 per cent of those with headache but only 11.3 per cent in those with no headache.

The relationship of nasal symptoms to headache is graphically illustrated in Fig. 1.

NASAL SYMPTOMS VS. HEADACHE

If we divide the cases into the different groups, first of all into those with nasal symptoms and then into those with no nasal symptoms, we see the incidence of headache as shown in Table II.

We see again in Group IV (the total group) that the incidence of headache varies greatly with the presence or absence of nasal symptoms. We see that in those with nasal symptoms, 83 per cent have headache, whereas in those with no nasal symptoms, only 55.6 per cent have headache.

Therefore, it is obvious that there is an undeniable association between headaches and the amount of nasal symptoms of any type. Whether these nasal symptoms are mainly allergic or not is a question which cannot be answered by numbers alone.

HEADACHE STATISTICS—OGDEN

Another point of possible interest concerns the type of nasal symptoms present in those individuals who do not have headaches. This is shown in Table III.

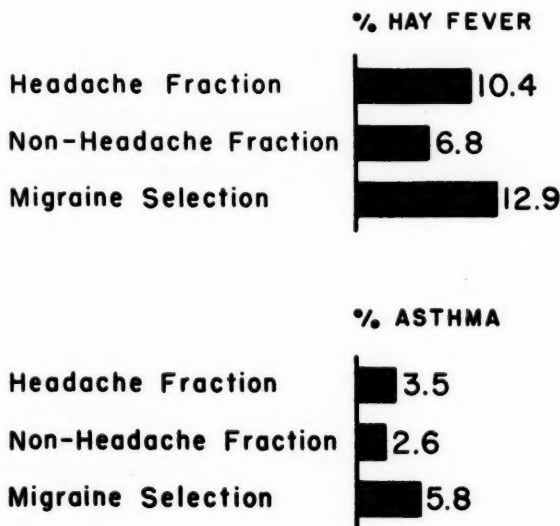


Fig. 2. Respiratory symptoms and migraine.

A comparison of these numbers with the previously reported data for the headache and nonheadache fractions of the various groups,¹ shows that in the above figures for those with no headaches but with nasal symptoms there is a greater tendency to the more acute type of nasal symptoms. In the headache fractions the percentage of those reporting more chronic symptoms such as blockage, postnasal drip, and sinus trouble is relatively higher.

While it is granted that many of these nasal or respiratory symptoms are not necessarily allergic, experience shows that the allergic mechanism is responsible for a great deal of chronic or recurrent respiratory disease.

To sum up, it is felt that consideration of all of the above data indicates that there is a greater amount of allergic disease among those with headache as compared with those without headache.

We had definite information concerning the sites of head pain. It was found that pain in the frontal area is present in 72.7 per cent of those with headache. It was also possible to correlate the location of head pain with certain criteria.^{1,2,3}

Migraine, when rigidly defined, was found in 5.2 per cent of those with headaches. If migraine was more loosely defined, it was seen to occur in 13.2 per cent of those with headaches.²

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The relationships of migraine and of all types of headache to asthma and hay fever are illustrated in Figure 2.

Additional data relating to frontal headache and migraine have been reported.³ It has not been previously emphasized that frontal headache is the most common variety. Therefore, the therapeutic management of this type of vascular headache warrants discussion.

It is felt that frontal headache is of the vascular type, since we have observed that many of the phenomena commonly associated with vascular headaches are present in this condition. These manifestations include prodromal symptoms such as *aurae*, visual difficulties, nausea and even vomiting, throbbing type of headache, *et cetera*. Also, in a recent study I found that the ergotamine drugs are effective in an impressive percentage of cases of frontal headache.⁴ The ergotamine drugs are known to be exceptionally helpful as vasoconstrictors of cranial vessels. While some may feel that the response seen in individuals with frontal headache is due to nasal decongestion, the author feels that it is due to the direct constricting effect of the ergotamines on arterial musculature.

In the same publication, we advanced the theory that possibly frontal headache is due to dilation of the anterior meningeal vessels. These vessels are terminal branches of the ophthalmic arteries, after they have given off the anterior and posterior ethmoid vessels which supply the nose. The idea is propounded that the dilation of the anterior meningeals is essentially due to a reflex mechanism in which the pressure of the nasal mucosa "triggers" or initiates the dilation. The response to the ergotamines certainly supports this view, as does also the relief obtained from the antihistamines and vasoconstrictor solutions in the nose. It should be re-emphasized that pain originating from the nasal mucosa or sinuses is not particularly referred to the frontal area. The old idea of the vacuum type of headache is no longer generally accepted.

It is of interest to note that patients with frontal headache occasionally complain of edema of the eyelids.

Realizing that frontal headache is often ascribed to visual difficulties, data were obtained showing the relationship in per cent of this type of headache, nasal symptoms, and any type of visual disturbance (Table IV).

Thus, it may be seen that there are more visual difficulties during and before attacks of frontal headache in those individuals who also have nasal symptoms. On the other hand, there was in the main, no difference in the per cent of those with visual symptoms before attacks of headache in the two selections.

In another publication³ we reported the per cent incidence of the same visual difficulties in all types of headache, frontal headache, and migraine. In Table V, only group IV figures are listed.

We therefore see that there are more visual disturbances reported in the migraine syndrome than in other types of headache. This does not

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TABLE IV

Visual Disturbances	Group I		Group II	
	No. cases frontal headache 1715		No. cases frontal headache 157	
	Nasal symptoms	No nasal symptoms	Nasal symptoms	No nasal symptoms
Before headache	3.7	3.1	1.4	2.3
During headache	26.2	19.6	28.2	9.3
Both before and during	9.1	4.7	7.0	...
None	60.9	72.6	63.4	88.4

Visual Disturbances	Group III		Group IV	
	No. cases frontal headache 312		No. cases frontal headache 2184	
	Nasal symptoms	No nasal symptoms	Nasal symptoms	No nasal symptoms
Before headache	0.5	2.6	3.0	3.0
During headache	31.3	14.9	27.3	18.4
Both before and during	9.2	2.6	9.0	4.1
None	59.0	79.8	60.7	74.5

TABLE V

Visual Disturbances	All types headache	Frontal headache	Migraine headache
Before headache	2.8	2.9	5.8
During headache	20.0	22.5	29.0
Both before and during	6.1	6.4	18.1
None	70.2	68.1	47.1

disprove the vascular mechanism of frontal headache, since we know that in general there is a more severe degree of symptoms in typical migraine.

While an evaluation of these data cannot establish the degree of importance of errors of refraction, or of any visual difficulty in the causation of headache, it is the opinion of the author that eye changes are often falsely termed as a specific causative factor. It is felt that eyestrain may act as a nonspecific aggravating cause and may bring on an attack in a headache-susceptible individual with a labile vasomotor mechanism of the cerebral vessels. It is the experience of ophthalmologists that headaches may be temporarily relieved after refraction and the use of suitable glasses. However, in many cases after a varying period of time the headaches return in their former intensity. There is no question, of course, that suitable glasses should be used if necessary.

It has been universally recognized that the common recurrent type of headache (the vascular type) is directly related to the increased amplitude of pulsation of arterial vessels. These vessels may be intracranial or extracranial.

The lability of the vessels is thought to be affected by a number of factors.

1. Vasodilator substances. This includes histamine, alcohol, nitrites, bus fumes, et cetera.
2. Occupational or situational tensions.

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3. Mental upsets and various psychogenic states.
4. Nonspecific factors, including temperature changes, fatigue, possibly eyestrain, et cetera.
5. Endocrine. The physiologic changes attendant to menstruation may initiate headache. Another cause also may be present, menstruation acting as the "trigger."
6. Hypertension.
7. Reflex. Headache possibly due to dilation of the anterior meningeal arteries may be essentially reflex in character.
8. Mental conditioning. The patient may associate a chain of events or circumstances with the onset of headache. These pains regularly may appear at these times.
9. Allergy. The above statistical data indicate the presence of an allergic mechanism in many cases.

The above discussion does not include organic causes of headache, such as neoplasia, trauma, acute sinusitis, simple myalgia, neuralgia, et cetera.

Let us now discuss the management of headache:

SYMPTOMATIC

- a) Ergotamines—when used properly, cause constriction and relief of pain in most instances; also helpful in frontal headache.
- b) Antihistamines—definitely helpful in the frontal type.
- c) Nose drops—useful at times when nasal symptoms are present.
- d) Analgesics—merely mask pain temporarily, but do not act as vasoconstrictors.
- e) Nicotinic acid—effect variable.
- f) Oxygen—effect variable.
- g) Octin—said to be efficacious in many cases.
- h) Other vasoconstrictors—ephedrine, epinephrine, caffeine—effect variable.

ADJUNCT

- a) Refraction and the use of eyeglasses if needed.
- b) E.N.T. management and the correction of any nasal abnormalities.
- c) General medical.
- d) Miscellaneous (dental, orthopedic, endocrine, et cetera).

PREVENTATIVE

- a) Psychiatric. Mental, emotional, and situational problems should be properly handled. Headaches may be initiated merely by a chain of events or circumstances.
- b) Allergic. Headaches, especially those of the frontal type, may be due to sensitization to inhalant antigens. Food allergy may also

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- cause frontal headache, and has long been recognized to be an important factor in migraine. Bacterial sensitization may play a part.
- c) Proper handling of other contributing or nonspecific factors (as listed above, under factors influencing lability of vessels).

ACKNOWLEDGMENT

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BLOOD NEEDS ARE GREAT

"Where is the man to be found who wishes to remain indebted for the defense of his own person and property to the exertion, the bravery, and the blood of others, without making generous effort to repay the debt of honor and gratitude."

—GEORGE WASHINGTON

The National Blood Program Publication Manual contains a great deal of background information which presents the Fact Sheet, Action, Publicity, etc. This manual may be obtained by writing to National Blood Program, Office of Defense Mobilization, Executive Office of the President, Washington 25, D. C.

Confronted with the growing blood needs of the country, the President recently recognized blood as a national resource by placing responsibility for the co-ordination of all blood activities in the Office of Defense Mobilization. The National Blood Program is charged with meeting the entire blood needs of the nation.

The total blood needs are great: blood is needed for current use by the Armed Forces; it is needed to fill the immediate requirements of civilians; and above and beyond these daily needs, there must be blood for a national plasma reserve ready for use in any emergency, civilian or military, which might arise. To fill all of these important and continuing needs, the National Blood Program needs your support in persuading the American people to become regular blood donors.

PAUL GAYNOR, *Co-ordinator*
National Blood Program

THE USE OF MEAT AS THE SOURCE OF PROTEIN IN MILK SUBSTITUTES IN ALLERGIC GASTROINTESTINAL DISORDERS OF EARLY INFANCY

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THE reasons for and the logic of using strained meat as the source of protein in milk substitutes for infants apparently intolerant of both cow's milk and soy bean milk were reviewed by Glaser¹ in 1943 and 1944. At that time, several infants with atopic dermatitis (eczema) in the above category were reported who responded favorably when "meat milks," prepared according to a formula worked out by Rowe,* were employed. The use of the somewhat awkward term, "meat milk," seems appropriate since an analogous term, "soy bean milk," is now accepted as good usage. In recent years, a number of infants in the newborn period† and in very early infancy without atopic dermatitis, but with gastrointestinal disturbances apparently due to allergy to cow's milk which did not respond to substitution to soy bean milk, have been studied. These infants were, however, successfully treated with meat milks. Since these cases were not indexed as such in our diagnostic files until the past six months, it is difficult to state, at this time, how many we have so studied, but we estimate an average of four to six yearly as a minimum. Since our practice as regards the newborn and very young infants is limited to children in allergic families, our incidence is doubtless considerably higher than in a general pediatric practice. Nevertheless, two of the three cases here reported were brought to us because relief had not been obtained in the hands of the family pediatrician. These cases are those most recently seen and illustrate the essential features involved.

The formula for the preparation of the meat milk is illustrated in Table I, which is a copy of the instructions given to the mother of the infant. It differs only in minor details from that previously employed, the principal difference being that it is cooked for a total of only twenty minutes instead of forty-five as in the past. These directions are slightly modified from those of Rowe⁵ according to his most recent publication on this subject. In recent years, because of their ready availability, we have

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*Personal communication to the senior author at that time.

†The first thirty days of life, according to definition by the Committee on Fetus and Newborn of the American Academy of Pediatrics, *J. Pediatrics*, 28:244, 1946.

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TABLE I. SUBSTITUTE FORMULA FOR COW'S MILK CONTAINING
STRAINED MEATS (ROWE)

Strained lamb	1 cup (8 oz)
Oil (use one of these) :— sesame; olive; corn (Mazola)	3½ tablespoons
Ordinary table sugar	2½ tablespoons
Starch (use one of these) :— potato; tapioca; rice; arrowroot	2 tablespoons
Calcium carbonate (Get 4 oz from your druggist— prescription not necessary)	1 teaspoon
Ordinary table salt	½ teaspoon
Water	4 cups (32 oz)

All measurements are level, using standard measuring cups and spoons.

Heat water in the top of a double boiler until the water in the outer boiler starts boiling. Add the salt, sugar, and calcium carbonate.

Mix the starch to a paste in one third cup of cold water and stir into the water in the top of the double boiler.

Cook mixture for ten minutes in the top of the double boiler, stirring constantly to prevent lumping.

Then add the strained meat and oil and make up to one quart, if the total volume is less, with boiled water. Mix thoroughly and cook for ten minutes longer. Bottle and use as formula.

used only the strained meats put out by Swift, viz., lamb, beef and pork. However, there is no reason why similar preparations by other companies should not be used, and we have also employed the meat of chicken, previously boiled and treated in a Waring Blendor in the manner described by Stuart⁶ for preparing strained meats at home. These meat milks, which are essentially soups, have a very fine taste and are readily accepted by the infant. We prefer to use lamb, since, in our experience, infants show less clinical sensitivity to this than to any other of the commonly used meats except, possibly, rooster or capon. We use the male fowl because it is possible that there may be enough egg protein in the blood in the tissues of the female to cause reactions in individuals who are exquisitely sensitive to egg white. Such cases have been reported in adults by Rinkel, Randolph and Zeller.⁴ Egg white sensitivity is common in allergic eczematous infants and, by inference, in infants of the same age group with other manifestations of allergy, although we have made no specific study of this problem.

The following are illustrative case reports:

Case 1.—(No. 10854) This boy was first seen at the age of seven weeks because of very severe colic which had started at the age of three weeks. The customary methods of treatment and various cow's milk formulae gave no relief, so he was tried on soy bean milk, also without improvement. When first seen by us, the baby was in good physical condition and weighed 3,900 Gm (8 lbs, 9 oz). At this time, besides colic, the child now had very watery stools from which no pathogens could be isolated. The usual methods for the treatment of diarrhea gave no relief. When he was put on lamb meat milk, his improvement was steady and rapid and he was symptom free within thirty-six hours. Other foods were gradually added as the

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child grew older, and it was eventually discovered that a significant number (apples, apricots, beef, peas, pears and prunes) caused either a rash or colic. This was confirmatory of our original diagnosis of colic due to food allergy. A curious development in this case was the appearance of a large patch of alopecia areata at the age of ten weeks, which, however, was almost healed by the time the child was six months of age, at which time he was last seen. He was doing well on the lamb meat milk and weighed 8,000 Gm (17½ lbs), about 240 Gm (8 oz) more than the average infant of his age and length. It is planned to attempt a transfer to cow's milk formula at the age of eight months.

Case 2.—(No. 10422) This boy was first seen within a few hours after birth. His father had suffered, though not very seriously, from various allergies throughout his life. Of his two siblings, one brother suffered severely, and still does at the age of twenty-four years, from chronic atopic dermatitis (eczema) and bronchial asthma. The remaining brother had been severely incapacitated from early childhood until manhood because of unrecognized food allergy, mistakenly diagnosed by gastroenterologists of national reputation as terminal ileitis. It may well be imagined that, as a lifetime habitué of our office, the father was familiar with our interest in the prophylaxis of allergic disease in the newborn period and early infancy, and lost no time in putting his infant under our care immediately after birth. The mother, who was able and willing to nurse the baby, was placed on a controlled diet, limited as to egg and milk, with supplementary minerals, as has been previously described.² As a complementary feeding for the prophylaxis of cow's milk allergy,³ soy bean milk was prescribed. The mother, on leaving the hospital, reported that the child did well, so we did not see him again until he appeared at the office at the age of one month. At this time we were truly alarmed by the infant's appearance. He had weighed 3,426 Gm (7 lbs, 2 oz) at birth and, since then had gained only 278 Gm (9 oz.) and looked scrawny, almost cadaverous. Perhaps the reason the parents were not alarmed by the child's appearance was that the paternal grandmother kept insisting that the father had looked just the same way at this period of infancy. Knowing his history of allergy, we had no doubt regarding the truth of her observations, but thought that we ought to be able to do better with the infant than that. The supply of breast milk had started to diminish at about this time, so we continued the boy on soy bean milk, which he appeared to take in adequate amounts; nevertheless, he failed to gain. Within a week, he was down to only 64 Gm (2 oz) above his birth weight. He did not appear dehydrated, but was emaciated and drowsy most of the time, somewhat suggesting adrenal insufficiency. He was taken completely off the soy bean milk and the breast, which was now in very scant supply, and put on lamb meat milk. He took this well and immediately began to thrive, developing a truly remarkable appetite, soon averaging 300 cc (10 oz) at a feeding. By the time he was ten and one half weeks old, a period of somewhat more than four weeks on the meat milk, he had gained 1,705 Gm (3¾ lbs) and weighed 5,000 Gm (11 lbs), only 240 Gm (8 oz) below the average normal for his age and length. His progress was steady and rapid. At the age of three months, a geographical tongue was noted, tending to confirm our diagnosis of an allergic child. At the age of six months, he developed diarrhea, suspected of being due to *Salmonella choleraesuis*, although this was found on only one occasion. He recovered from this spontaneously, as the antibiotic prescribed was, through error, not administered. When last seen at the age of nine months, he was still gaining nicely and weighed 9,020 Gm (19 lbs, 12 oz), which was slightly below the average for his age and length, probably on account of the protracted enteral infection. It is our plan to keep him on the lamb meat milk until he is a year of age.

Case 3.—(No. 10939) This boy, whose birth weight was 3047 Gm (6 lbs, 10 oz),

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was the first child of a middle-aged couple. His father had pollinosis. The baby did well in the hospital on a cow's milk formula and went home with his mother at the age of five days. The day following discharge, he developed diarrhea and vomiting, and, at the age of eight days, was readmitted to the hospital because of dehydration. Twelve hours after admission, his temperature rose to 39.5° C. (103° F.), but came down to normal twelve hours later. Hemolytic *staphylococcus albus* and *Hemophilus influenza*, both of which were sensitive to terramycin, were recovered from his nose and throat. No pathogens were obtained on stool culture. He was kept on terramycin throughout the hospital stay. After the diarrhea and vomiting had ceased on therapy of starvation and parenteral fluids, he was started on soy bean milk because it was felt that the previous cow's milk formula had probably resulted in his gastrointestinal disturbance. On the soy bean milk, he again developed vomiting and diarrhea. This formula was stopped and water substituted, which he retained, and the diarrhea and vomiting also ceased. Nutramigen was started and he did well on this for twenty-four hours, when again vomiting and diarrhea developed. As soon as this had ceased after the Nutramigen was stopped, he was put on the lamb meat milk formula. Gastrointestinal symptoms did not recur, and during the remainder of his hospital stay, a period of four days, his weight increased from 2,775 Gm (6 lbs, 1½ oz) to 3,175 Gm (6 lbs, 14 oz), a gain of 400 Gm (12½ oz). At the age of four months, he was uneventfully gradually changed to an evaporated cow's milk formula. We would have liked to keep him longer on the lamb meat milk, but, because of the mother's desire to feed her child as other children were fed and our own curiosity to see whether or not he would be able to tolerate a cow's milk formula at that age, he was placed on the evaporated cow's milk formula.

CONCLUSIONS

From the study of the three cases above reported, as well as many others previously studied and not as yet reported, we conclude that the use of meat as the source of protein in allergic gastrointestinal diseases during the newborn period and early infancy, when these conditions are due to allergy to cow's milk or allergy or intolerance to soy bean milk, is a practical and useful procedure. When relief is obtained by the use of meat milks, it is striking and rapid, and occurs within the first twenty-four hours of use.

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INFLUENCE OF TONSILLECTOMY AND ADENOIDECTOMY ON CHILDREN WITH SPECIAL REFERENCE TO THE ALLERGIC IMPLICATIONS ON RESPIRATORY SYMPTOMS

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IT has been estimated that as many as 2 million operations for removal of tonsils and adenoids are performed in an average year in this country. This comprises approximately one-third of the total of all types of surgical intervention. Good results following removal of the tonsils and adenoids in selected patients have encouraged recommendation of this procedure for many children—often, however, without definite indications. If the operation is performed primarily to correct an undiagnosed allergic state, to “fatten a thin child,” or “to improve a poor appetite,” success will be the exception rather than the rule. As for the influence of tonsillectomy and adenoidectomy on respiratory tract infections in children, the generally accepted view is that the operation has a beneficial effect if performed for sound reasons.

Statistics of the U. S. Children's Bureau⁶ show a gradually decreasing incidence of the mortality and morbidity of those diseases complicating upper respiratory tract infections. This trend, although not so rapid, was noticed by many physicians who were in active practice even before the sulfonamides and the antibiotics were made available.

It is generally believed that the removal of infected, hypertrophic tonsils and adenoids has been partially responsible for the gradual improvement in the health of children in the United States. It is difficult to evaluate such a claim accurately, because of the many factors involved. These include the child's age, type of diet, clothing, shelter, other illnesses, fatigue and rest, undue exposure, and emotional disturbances. All of these and probably many other factors influence the course, complications, and prognosis of tonsil and adenoid diseases. Our impressions are based on not only our own active experience but also that of other clinicians who have had the opportunity to observe large numbers of patients over long periods of time. In an effort to analyze the effect of tonsillectomy and adenoidectomy on respiratory tract symptoms in children, several aspects of the problem must be duly considered.

INDICATIONS INFLUENCE RESULTS

“My child has one cold after another.”¹ This is a frequent complaint from mothers and is probably the major reason why many children are

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subjected to tonsillectomy. Parents of these children often become dissatisfied because the operation does not correct the original complaint: others, again, are pleased with the outcome. The children who are improved usually are those whose indications for the operation fall in the following list of symptoms:

1. Repeated tonsillitis, usually with fever;
2. Cervical adenitis following sore throats;
3. Otitis media, acute, chronic or recurrent, secondary to infection of the upper respiratory tract;
4. Systemic infection and/or poor nutrition resulting from repeated attacks of tonsillitis;
5. Nasal obstruction and mouth breathing from obstructive adenoids, (often associated with impaired hearing and facial asymmetry);
6. Abscess of the pharynx, tumors or injuries of the tonsils, and fetor oris from debris in the crypts of these structures.

To the parent the term "cold" may include any or several of the above indications, and even a few more. These infections may not only unfavorably influence the physical and mental growth and development of the child, but also activate certain constitutional disorders. It is not uncommon for the symptoms (as listed) to recur several times a year, usually in the winter months when respiratory tract infections are more prevalent. If absolute indications exist, surgical removal of the tonsils and adenoids in children is followed by a gratifying result. Furthermore, relief of symptoms occurs within a short period of time.

UNFAVORABLE RESULTS DUE TO UNRECOGNIZED ALLERGY— CONTRAINDICATIONS

In a fairly large percentage of children who undergo tonsillectomy for one reason or another, the outcome is not favorable.² In fact, the symptoms often become more pronounced than they were before operation. In many of these unsuccessful cases the underlying cause may be other than that of infection, although the major symptoms are the same. In this connection it can be said that previously unrecognized or untreated allergies are largely responsible (more than any other reason) for the poor results following tonsil and adenoid surgery. The nasal and pharyngeal symptoms attributable to allergic disease do not seem to be relieved by surgical intervention.

The allergic child has one or all of the following symptoms:

- (1) "Catches one cold after another," with or without fever.
- (2) "The nose is 'runny,' 'stuffy,' more pronounced at night and in the morning, clearing up during the day." These symptoms may be seasonal or perennial, and are often associated with mouth breathing, sneezing, sniffing, or poor hearing.
- (3) Cough is more prominent at night, on lying down, or following

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exertion, worse in the summer than in the winter, and usually occurs periodically every year. Headache, fatigue, listlessness, and irritability may be associated with any of the above symptoms. A review of these symptoms immediately points to their allergic nature.

Chronicity and *periodicity* characterize allergic disease. Symptoms of colds that are worse at night or on awakening than at any other time of the day, or worse during certain times of the year or in certain places, or which occur every time school starts or during each winter or every summer when plants are blooming, are usually of an allergic nature. A carefully taken history often reveals that the parents are allergic and may have similar symptoms.

The effects of the operation may be harmful instead of beneficial. Asthma has been precipitated by the removal of tonsils and adenoids in children with seasonal hay fever, especially during the pollen season. Experience has demonstrated that local allergic manifestations in the nose and throat are not corrected by this operation. It is, therefore, important to consider that in some children allergy may be a contraindication for tonsillectomy. It is desirable to treat the allergic symptoms first, and when the allergy is under control, then consider the removal of the tonsils and adenoids. This operation should be performed only if there are the same indications as in a nonallergic child. Frequently, the tonsils and adenoids will become smaller when relief has been obtained by thorough allergic management. As there are no set rules to be followed, the situation resolves itself into one of individualizing the decision to be made, carefully weighing the indications and contraindications. While the allergic child may need his tonsils and adenoids removed because of recurrent attacks of sore throat or for other plausible reasons, relief of the allergic symptoms should not be anticipated. It is reasonable to assume, however, that the child's general health will be improved because he is freed from an infectious process. These facts should be made clear at the outset to the parents, so that there will be no subsequent disappointment on the part of those concerned. After the operation, specific allergic diagnosis and treatment should be continued to relieve the allergic symptoms. It is essential to stress the latter.

It has been stated that following tonsillectomy and adenoidectomy some children are predisposed to more frequent attacks of bronchitis and pneumonia. This has been found to be true only in allergic persons. They probably would have fared better if their tonsils and adenoids had been left intact and if they had benefited by specific allergic therapy prior to any such operation.

FAVORABLE EFFECTS

General.—Kaiser,⁵ in a ten-year study of 4,400 children for whom tonsil and adenoid operations were advised, made some enlightening obser-

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ventions. Over 50 per cent of the patients improved in general health, and normal growth and development were favorably influenced. Children subjected to operation had less severe sore throats and fewer bad colds, purulent ears and swollen glands than those of an unoperated group. Those who were not benefited may have been suffering from some sort of allergy. This is not an unreasonable assumption, as the group included children with "*recurrent, chronic* attacks of head colds, laryngitis, croup, sinusitis, asthmatic bronchitis, and pneumonia"—all of which may be allergic and not usually characterized by infectious manifestations.

Rheumatic Fever.—It is generally agreed that acute infections of the throat, particularly of the tonsils and adenoids, predispose to rheumatic fever in certain susceptible children. Kaiser, in his long-range study of 4,400 children, concludes that the incidence of acute rheumatic fever was less in a group of tonsillectomized children than in those who still had their tonsils. Apparently the removal of tonsils and adenoids in those who suffer from chronic rheumatic fever does not seem to materially influence the course of the disease.

Cervical Adenitis.—Tonsillectomy and adenoidectomy represent the treatment of choice for the prevention of recurrent cervical adenitis incident to tonsillar infection. Since the introduction of the sulfonamides and antibiotics, there have been substantially fewer cases of abscessed cervical glands requiring incision and drainage. This newer therapy does not, however, influence the incidence of tuberculous cervical adenitis, for which tonsillectomy and adenoidectomy is still the most effective procedure. It has been noted that this condition occurs less frequently in tonsillectomized children as compared with those whose tonsils have not been removed.

Otitis Media—Hearing.—Otitis media and impaired hearing are intimately related to the tonsil and adenoid problem, especially in pre-school age children. Those from one to six years of age who suffer from repeated ear infections belong to the group most benefited by the removal of tonsils and adenoids. In this latter group this operative procedure will also lessen the incidence of subsequent upper respiratory tract infections which may lead to complicating diseases.

Children with chronic discharging ears are usually cured of such involvement only after removal of large and infected adenoids. Improvement of hearing is a dramatic occurrence after a brief period of time. Those who are not benefited are invariably found to suffer from an associated untreated allergic rhinitis. Chronic allergic edema of the tissues of the postnasal space and eustachian tubes continues despite operation and is responsible for the persistence of symptoms. Intermittent deafness is often due to allergic edema. Children with "adenoid facies" due to markedly enlarged

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and infected adenoids may often show facial asymmetry and distortion of the jaws. These unnatural anatomical changes revert to normal following tonsillectomy and adenoidectomy.

GROWTH AND DEVELOPMENT

The general nutrition, growth, and development of the child may be delayed or unfavorably disturbed by repeated infections of the tonsils and adenoids. Despite opinions to the contrary, focal infection may cause pyelitis, nephritis, septicemia, arthritis, and other serious illnesses. These complicating diseases do not seem to occur as often or as severely after the tonsils and adenoids have been removed. It is not unusual to note a return to normal physical growth and development following a tonsil and adenoid operation. There is marked improvement also in the child's mental and psychological state. It has often been observed, especially in pre-school children, that they are happier and more cheerful after removal of the diseased lymphoid structures of the pharynx. The dull feeling, fatigue, and general irritability common in children with hypertrophic infected adenoids and tonsils is relieved within a short time following operation.

WHY TONSILS "GROW BACK"

Tonsils which "grow back" may account for the continuance or return of symptoms for which they were originally removed.² While there may be several causes for regrowth, there is ample evidence that in many instances it is attributable to incomplete surgery.⁴ Where the surgical technique has been excellent and lymphoid regrowth occurs either in the tonsil fossa or posterior pharynx, one must search for an allergic etiology. This diagnosis will usually explain the symptoms, which are corrected after institution of allergic therapy. As has already been emphasized, tonsillectomy and adenoidectomy will not influence allergic manifestations and symptoms. The author has found (in a twenty-year study) that among allergic children whose allergy was undiagnosed or untreated, 30 per cent had lymphoid regrowths in their tonsil fossa or pharynx following adequate tonsillectomy and adenoidectomy. This compares with a figure of only 3 per cent in nonallergic tonsillectomized children. This also explains, in part at least, why even repeated operations for the same condition fail to relieve the original symptoms. In other words, it is most important to treat the allergic symptoms first, before good results can be expected in this group of children.

THE AGE FACTOR

The age of the child who needs his tonsils out often comes up for consideration. There is no valid reason for setting an age limit, as the problem at all times is an individual one. This operation can be performed at any age, if in the physician's judgment the child will benefit from the

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operation. The common belief that the operation at any early age predisposes to recurrence is not valid. The criterion is an adequately performed operation in a nonallergic child. It has been our practice in the Children's Clinic, Seattle, for the past twenty years, to remove the tonsils and adenoids in a child at any age when we believe that absolute indications are present and that the child will be benefited by the operation.

Finally, neither age nor season of the year should be allowed to influence the situation. There has not been any conclusive evidence that this operation predisposes to poliomyelitis.³ The important consideration is the precise need for surgical intervention. It should not be "artificial" in the sense that the indication are made to justify the procedure. Rather, the indications should be definite, obvious, and well-recognized. Under such circumstances, the age of the patient is no more a factor in tonsillectomy than it would be in appendectomy. If the operation will benefit the child, other factors which might contraindicate the operation can well be disregarded.

SUMMARY

The operation for removal of tonsils and adenoids should be performed for adequate indications in any child whom the physician feels will be benefited by this procedure. Most failures are due to the fact that similar symptoms of allergic etiology are overlooked. Correct diagnosis of the allergic disease followed by thorough, specific treatment will often prevent this operation, as well as certain common complications.

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BRONCHIAL ASTHMA IN CHILDREN: TREATMENT AND RESULTS

A Thirty Year Study

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IN 1942, two of us (L. U. and A. A. W.) spoke before the Section on Medicine of the American Medical Association. Our subject was "Bronchial Asthma: Survey of Value of Treatment in 459 Cases During Twenty Years."^{15,17} At that time we said that "the practice of allergy has developed into a major medical science within the past twenty years."

TABLE I

As a part of an intensive study on asthma in children, it becomes important to know what has become of you since we last saw you in _____. We would appreciate it if you and/or your parents would answer the following questions as accurately as you can:

1. Have you had any asthma since we last saw you? _____
 A. If so, has it been mild, moderate or severe? _____
 What time of year? _____
 Are you well between attacks? _____
 Have you required adrenaline (specify spray or injection)? _____
 B. If you are cured, when did the asthma leave you? _____
 C. Are you now exposed to any particular kinds of dust? _____
 If so, specify _____
 To what animals are you exposed? _____
 What kind of pillows have you? _____ Mattress? _____
 Have you nonallergenic covers on your mattress and pillows? _____
 2. Have you taken treatment for asthma from some other physician? _____
 A. If so, what sort of treatment? _____
 B. What were the results? _____
 3. Have you had nasal polyps since we last saw you? _____
 4. Since we last saw you, have you changed climate because of asthma? _____
 A. If so, when and where did you go, and how long did you stay? _____
 B. What were the results? _____

In any case, we are anxious to know about you and we request that you use the back of this letter to write any additional information about yourself and your asthma. All this will be of great service to those who suffer from asthma. We would appreciate it if you would return this letter with your answers promptly in the enclosed stamped envelope. Also, please let us know your present address.

In that study and in the present one, no patient was included unless at least one year had elapsed since treatment was started. This period of observation now ranges up to thirty years. Private patients have been used in both studies because of better co-operation and more reliable information.

Our information was obtained by several methods. This was easy in patients who are still under observation. For patients no longer under our care we mailed questionnaires (Table I), with a return, self-addressed, stamped envelope. We received a fairly large number of answers. In some

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TABLE II. CLINICAL CLASSIFICATION

Name:	Age at Onset	Sex	Age	First Seen
Address:	Occupation	Source	Last Seen	
HISTORY	EXAMINATION	Wt.	B.P.	RESULTS
I Attacks	Type			Duration of cure
Cause onset	Chest deformities			Condition
Course	Cyanosis			Since last seen
Season	Lungs			At present
Duration	Wheezing			Adrenaline
Frequency	Prolonged expiration			Exposure to animals and
Cause of attacks	Emphysema			feathers
Relieved by	Heart			Treatment by other M.D.
Other	Other findings			Kind
	X-ray chest			Results
	Eosinophilia			Surgery
II Between attacks	Blood			Results
Dyspnea	Sputum			Change of climate
Cough	Skin tests			Length
Expectoration	Cutaneous			Location
Other	Intracutaneous			Results
Environmental factors	Nose, throat, teeth			
Occupational factors	Previous operations			
Food idiosyncrasies	Findings			
Drug idiosyncrasies	TREATMENT			Results in %
Previous tests and results	Elimination of			REMARKS:
Previous treatment	Desensitization to			
Change of climate	Vaccine			
Family history	Drugs			
Past history	Removal foci			
	Other treatment			
	Duration treatment			
	Co-operation			

TABLE III. RESULTS OF TREATMENT IN 306 CASES OF BRONCHIAL ASTHMA IN CHILDREN

Type of Asthma	Age at Onset	Symptom-free		Marked Improvement		Moderate Improvement		No Improvement		Dead	
		No.	%	No.	%	No.	%	No.	%	No.	%
I. Paroxysmal (281 cases)	Before 1	15		20		4		1		1	
	1-2	28		46		9		4		1	
	3-4	20		29		8		1		1	
	5-7	20		24		12		3		0	
	8-10	6		10		1		2		0	
	11-13	8		3		3		0		1	
	Total	97	34%	132	47%	37	13%	11	4%	4	1%
II. Chronic (25 cases)	Up to 13	2	8%	7	28%	8	32%	4	16%	4	16%
Total (306 cases)		99	32%	139	45.5%	45	14.7%	15	4.9%	8	2.6%

cases we were helped by personal telephone calls or by the physician who referred the patient. Unfortunately, we could not locate or did not hear from a large number of our former patients, both children and adults.

A summarizing card (Table II) was made out for each case, and this contains the important information for that patient. We are now reporting the results in 306 asthmatic children in whom symptoms began on or before the age of thirteen years.

Table III shows that we divided our cases into paroxysmal and chronic groups. Symptoms were paroxysmal in 281 cases, i.e. the symptoms came

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in attacks, with complete or almost complete freedom between spells. Chronic asthma occurred in twenty-five of these children. The table also shows that in forty-nine cases paroxysmal asthma began before the child reached the age of one, that most of these children began to wheeze before they were eight. Very few of our patients reported to us before the age of one.

The results of treatment are summarized in this table. Complete freedom from symptoms for at least a year occurred in 97 out of the 281 paroxysmal group (34 per cent). We cannot call these patients "cured," however, as their asthma might return if the patient were again exposed to the offending allergen, e.g., egg, dog or cat.

Marked improvement (75 to 95 per cent) occurred in another 132 of these children (47 per cent); in this group there was no asthma except for an occasional siege after undue exposure to an allergen or after a severe "cold." These children were completely well between these attacks and normal in every other respect.

Moderate improvement (25 to 70 per cent) was obtained in another thirty-seven cases (13 per cent). There was no improvement in eleven cases (4 per cent), and death (but not from asthma) was reported to us in four cases.

TABLE IV. CAUSES OF DEATH

	Number Cases
1. Asthma main or sole cause.....	3
2. Asthma a contributory factor.....	2
3. Not related to asthma.....	3
Total	8

The twenty-five children who had chronic asthma did not do too badly when we realize that emphysema was probably already present in every case. Symptoms ceased entirely in two cases, with marked improvement in seven and moderate in eight. There was no improvement in four cases. Death occurred in another four, due entirely or partially to asthma itself. Altogether, in both groups, there were eight deaths, and, as shown in Table IV, asthma was responsible in three cases and partially the cause in two others. One of these had pneumonia with asthma, the other acute laryngo-tracheobronchitis plus asthma.

Altogether, then, in these 306 asthmatic children, both paroxysmal and chronic, complete relief occurred in 99 cases (32 per cent), marked and moderate relief in another 184 cases (60 per cent), with no improvement in only fifteen (4.9 per cent), and death in eight (2.6 per cent). Incidentally, our statistics show that the results of treatment do not seem to be related to the age of onset of asthma in these children.

Let us compare these results with those we reported in 1942 (459 cases in both adults and children) (Table V). The prognosis in children is obviously much better than that in adults, and the outlook for those with paroxysmal asthma is much better than that in chronic cases.

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TABLE V. RESULTS OF TREATMENT IN 459 CASES OF BRONCHIAL ASTHMA*

Age at Onset	Paroxysmal				Chronic			
	Symptom-free	Improved	Unimproved	Dead	Symptom-free	Improved	Unimproved	Dead
0-9	55	81	5	3	—	23	9	5
10-19	9	29	6	—	2	13	9	4
20-29	17	27	4	2	—	8	10	4
30-39	8	17	5	1	—	11	7	6
40-49	4	17	—	3	2	7	9	11
50-59	—	2	1	2	—	9	4	4
60-69	—	—	—	—	—	1	—	3
Totals	93	173	21	11	4	72	48	37

CAUSES OF DEATH IN BRONCHIAL ASTHMA

1. Asthma main or sole cause 21 cases**
2. Asthma a contributory factor 16 cases
3. Other causes (asthma not a factor) 11 cases

**Morphine known to have been injected prior to death in six of these patients.

*From Unger, L., and Wolf, A. A.: Bronchial asthma: survey of value of treatment in 459 cases during twenty years, J.A.M.A., 121:325, 1943.

TABLE VI. CORRELATION OF DURATION OF ASTHMA WITH RESULTS OF TREATMENT

Duration of Disease (Years)	Symptom-free		Marked Improvement		Moderate Improvement		No Improvement		Dead		Totals
	No.	%	No.	%	No.	%	No.	%	No.	%	
Under 1 year	18	33%	22	41%	10	19%	3	5%	1	2%	54
1-2 years	26	36	32	44	8	11	4	5	2	2	72
3-4 years	18	27	31	46	13	19	3	4	2	3	67
5-7 years	22	29	40	53	9	12	3	4	1	1	75
8-10 years	10	38	10	38	4	15	1	4	1	4	26
Over 10 years	5	45	3	27	2	18	0	0	1	9	11

TABLE VII. CORRELATION OF ALLERGENS WITH RESULTS OF TREATMENT

Type of Prime Allergen	Symptom-free		Marked Improvement		Moderate Improvement		No Improvement		Dead		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	
Pollens	44	56%	19	24%	12	15%	3	4%	1	1%	79
Fungi	9	33	13	48	4	15	1	4	0	—	27
House or farm dust	23	36	25	39	12	17	3	5	1	1.6	64
Other inhalants	0	—	3	60	2	40	0	—	0	—	5
Foods	8	26	13	41	7	23	2	6	1	3	31
Multiple allergens	48	24	106	54	29	15	10	5	4	2	197
Negative skin tests	1	25	1	25	0	—	1	25	1	25	4

In Table VI we compare the results of treatment with the duration of asthma, and again there is no clear-cut tendency. The duration of paroxysmal asthma does not seem to alter the prognosis in children, but early onset of chronic asthma is a distinct handicap in both children and adults.

In Table VII it can be seen that the results of treatment do depend to a large extent on the nature of the allergen. In this chart, patients are classified according to prime allergen, although most patients were allergic to more than one group. Some children have been placed in two groups on this chart. Our best results were in the pollen-sensitive group. Forty-four of seventy-nine of this group became asthma-free, chiefly, we believe, by

injections of the specific pollen extract or extracts. Failure occurred in only three of this pollen group.

Our results in twenty-seven fungus cases were good, but only nine became completely free from symptoms for the trial period of at least a year. It can also be noted that 197 of these children were sensitive to more than one allergen. This multiple sensitivity is very common in asthma in all ages.

Foods were the prime cause of asthma in only thirty-one cases, or about 10 per cent. Our decision as to what constitutes an important allergen rests on the history, clinical trials, and skin tests. Skin tests help a great deal, but tests with food extracts are not as accurate as with inhalant materials. Those tests done by the scratch method are fairly accurate, especially with such foods as egg, fish and nuts. But those done by the intradermal technique require experienced personnel if they are to be accepted, and all positive reactions need clinical corroboration. We have repeatedly tried feeding tests in those children and adults whose history and skin tests did not help us to incriminate a food as a factor. However, these feeding tests, in our asthmatic patients, have not been of much help to us. Our 10 per cent incidence of foods as a prime cause of asthma in children is in sharp contrast with some other reports. Rowe and Rowe,¹² in 411 asthmatic children, found foods the sole cause in 50 per cent of those up to the age of five, and the sole cause in 26 per cent from five to twelve. Our percentages are more in line with those of Glaser⁵ and Hill.⁸ Foods are rather frequent secondary factors in these children.

It is interesting to note that negative skin tests occurred in only four cases, about 1 per cent. Our low percentage is probably due to the fact that we carry out about 200 to 250 scratch tests in each child. Following these, and when we have not obtained sufficient information, we do about twenty to fifty intradermal tests. Because of possible constitutional reactions, we never do an intradermal test until we have had a negative scratch test with that particular extract. Those who do fewer tests than we do, or those who do only scratch tests or only intradermal tests, will certainly miss some important positive skin tests.

Perhaps this might be a good place to state that it is our belief that while "colds" and other infections are important factors in bronchial asthma in children, their importance diminishes when the causative inhalant or food allergens are discovered and minimized or removed. We cannot agree with those allergists, Chobot among them,² who stress the great importance of infection. Our experience has been similar to that of most workers: i.e., that removal of tonsils and adenoids should be carried out only for the same reasons as in nonallergic children. We rarely advocate nasal or sinus surgery except for severe nasal obstruction.

Besides our 306 children who received treatment and were under our care, there were sixty more who were examined and skin-tested but who for one reason or another received no treatment. In Table VIII the sex

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and age of onset are given for the entire group of 366 children. For some unknown reason, boys predominated almost two to one. After puberty, this difference does not occur; in fact, chronic asthma in adults is more common in the female.

TABLE VIII. SEX AND AGE OF ONSET IN 366 CHILDREN WITH BRONCHIAL ASTHMA*

Age at Onset	Male	Female	Total
Before 1	33	17	50
1-2	81	39	120
3-4	44	34	78
5-7	46	25	71
8-10	18	10	28
11-13	14	5	19
Total	236	130	366

*60 children received no treatment.

TABLE IX. ASSOCIATED ALLERGIES (PAST OR PRESENT) IN 366 CHILDREN WITH BRONCHIAL ASTHMA*

	Number Cases
Atopic dermatitis (eczema).....	106
Seasonal allergic rhinitis (hay fever).....	128
Perennial allergic rhinitis.....	111
Urticaria and Angioneurotic edema.....	81
Allergic bronchitis.....	21
Nasal polyps.....	11
Gastrointestinal allergy.....	26
No associated allergies.....	68

*60 children received no treatment

Table IX shows the associated allergies, past or present, in these 366 asthmatic children. Atopic dermatitis (eczema) occurred in 106 cases and therefore deserves prompt attention from the allergy point of view because it is a forerunner of asthma. Seasonal rhinitis (hay fever) and perennial allergic rhinitis also commonly precede or accompany asthma. About 40 per cent of all patients with hay fever sooner or later develop bronchial asthma. In our experience, the perennial type of rhinitis is even more likely to end up in asthma, especially in adults.

Allergic bronchitis is characterized by spasms of cough without wheezing. In many cases it is a forerunner of true bronchial asthma.

DIAGNOSIS OF BRONCHIAL ASTHMA

The diagnosis is based on the following eight points:

1. It is an allergic condition with wheezing, dyspnea, orthopnea, and cough, associated with rhinitis and partial obstruction of the lower air passages. In paroxysmal asthma there are no symptoms between attacks; in chronic asthma there are some symptoms plus exacerbations.
2. Examination: wheezing, prolonged expiration in both lungs.
3. Fluoroscopy: diaphragm may be low; excursion decreased, especially during attacks.

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4. Eosinophilia usual: in blood to about 20 per cent; in sputum and nasal smears often higher (up to 100 per cent).
5. Relief from epinephrine and/or aminophylline.
6. Allergy in the family; other allergic conditions in the patient.
7. Any one of above findings can occur in nonallergic conditions.
8. *Skin tests important*: the physician must test for all possible inhalant materials plus foods eaten by the child. Important allergens may be missed if tests are incomplete. Scratch tests first are advised to prevent possible systemic reactions; intradermal tests should follow later if insufficient information has been obtained. Group tests should not be used, nor tests by commercial laboratories, as results must be correlated with the history of exposure and the clinical trials.

PREVENTION OF BRONCHIAL ASTHMA

Through inheritance, children of allergic parents frequently develop allergic conditions, including asthma. The following precautions will prevent or lessen this tendency:

1. To be avoided are dogs, cats, feathers and kapok (pillows, mattress, comforter, furniture), and stuffed animals.
2. The home must be as dust free as possible. A good vacuum cleaner with attachments is essential. Whisk brooms should not be used. Dust-proof covers over bedding, or rubber bedding, furniture, and rug pads, should be provided.
3. A dry basement lessens growth of molds.
4. Hypoallergenic cosmetics lessen exposure to orris root.
5. A child should have skin tests for pollens before he goes to camp. If positive, he should avoid camp during that pollen's season, e.g., ragweed.
6. New foods should be added one at a time, at least a week apart, to see if symptoms occur. Raw eggs should be avoided. Cooked foods are less allergenic than raw.
7. If mild symptoms develop, e.g., eczema, hay fever, sniffles, or recurrent bronchitis, a prompt and thorough allergy survey should be advised, including complete skin tests.
8. A child should be guided away from dusty occupations, e.g., farmer, furrier, baker, upholsterer, grain mill worker, florist, sandblaster, miner, domestic.
9. The child should avoid exposure to "colds."
10. Psychosomatic factors, if present, need proper attention.

The above precautions are important, and, if followed, the onset of asthma in these children can be prevented, or, if asthma does occur, the symptoms can easily be controlled. For further references on this subject, see articles by Peshkin,¹⁰ Unger,¹⁶ Glaser and Landau,⁷ and others.

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TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN

I. *Specific Treatment* gives best results:

1. *Avoid allergens*, e.g., dog, egg, fish, house dust. Complete elimination leads to complete relief from symptoms, i.e., clinical "cure." But, immunologically, "cure" rare as recurrence usually follows re-exposure.

2. *Hyposensitization* (desensitization): injections of increasing amounts of extracts of important allergens which cannot be avoided, e.g., house and occupational dusts, pollens, fungi, orris root. Results are usually good. Prolonged treatment is often necessary.

II. *Symptomatic Treatment*:

1. Reassurance is most important single measure.
2. Epinephrine (1:1,000) 0.20-0.40 cc; in oil; by spray.
3. Aminophylline rectally: 5 grains in 20 cc water (excellent).
4. Syrup ipecac: teaspoonful for severe attack; may repeat in one hour.
5. Ephedrine, potassium iodide, mild sedation, e.g., Benadryl.
6. Penicillin (or other antibiotic) for complicating infection.
7. Hospital (allergen-free room preferred) if attack lasts two days or longer.
8. Bronchoscopic aspirations may be life saving.
9. *Morphine or Demerol is contraindicated.*
10. Asthmatic children should be as active as other children but only to the point of their breathing capacities.

For further references see the excellent articles by Bowen,¹ Ratner,¹¹ Glaser,⁶ Salen and associates,¹³ Stoesser,¹⁴ Dees,⁴ Mirvish,⁹ and Clein.³

DISCUSSION

We have discussed the diagnosis, prevention, and treatment of bronchial asthma in children. Our tables show our results over the past thirty years. We believe our results are good, but we are not satisfied. We can go a long way in minimizing and perhaps preventing asthma. Progress will depend on further education of the medical profession and of the laity. We are especially indebted to the many pediatricians who have been pioneers in the field of allergy, and who in suspicious cases have urged early and thorough allergy surveys.

SUMMARY

1. This is a study of 366 children whose bronchial asthma began on or before the age of thirteen and who were studied for from one to thirty years.
2. In sixty of these cases, no treatment was given.
3. In the other 306 children, our results were as follows: complete relief of symptoms in ninety-nine cases (32 per cent); marked relief (75 to 95 per cent) in 139 cases (45.5 per cent); moderate improvement (25 to 75

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per cent) in forty-five cases (14.7 per cent); failure in fifteen children (4.9 per cent); and death in eight (2.6 per cent).

4. Paroxysmal asthma was present in 281 cases, with treatment giving far better results than in the twenty-five children who had chronic asthma.

5. Chronic asthma in children has a much better prognosis than that in adults.

6. The duration of paroxysmal asthma has no effect on the results of treatment; it is important in chronic asthma.

7. Results in pollen asthma were the best of all groups.

8. Foods were the main cause in only 10 per cent.

9. Atopic dermatitis and both seasonal and nonseasonal rhinitis were frequently associated with the asthma.

10. We have outlined our ideas regarding the diagnosis, the preventive measures, and the specific and symptomatic treatment of bronchial asthma in children.

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PROJECTIVE PSYCHOLOGICAL TESTS APPLIED TO THE STUDY OF BRONCHIAL ASTHMA

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SEVERAL years ago I became convinced that if emotional influences in bronchial asthma were to be understood, the physician should have several objective psychological tests as laboratory procedures to help him in this type of case. My inquiry was started by inserting more psychological questions into the patient's history. Of all known methods of study a personality history taken by a competent observer is probably the best guide to the emotional imbalances. Bennett Kraft⁷ and others employ very elaborate questionnaires successfully. It soon became apparent to me that many cases of severe bronchial asthma have multiple etiological factors and the emotional component may be large or small. A patient might have an asthmatic attack because he is sensitive to ragweed pollen, the next week because he has an infectious respiratory disease, and later because his girl friend has rejected him. This type of patient is difficult to treat and may become a chronic asthmatic, often developing status asthmaticus. Recently Brown,³ Franz Alexander,² Wittkower,¹¹ and others have emphasized the importance of both allergic and psychological methods in treatment. In spite of this combined treatment some of these patients require frequent admissions to a hospital.

Freeman⁴ states, "The psychosomatic patient shows particular constellations of somatic symptoms and personality traits capable of being experimentally measured and established as a distinct clinical entity. In other words, these symptoms occur together with sufficient frequency to constitute what would appear to be a psychosomatic syndrome." These psychosomatic patterns should be recognized by the allergist just as the allergic patterns are recognized.

This paper is a preliminary report in which twelve cases of severe asthma were studied by simple intelligence scales and personality tests. Two cases of bronchial asthma, well controlled, were included for comparative purposes. Previous to this approach other psychiatric procedures had been tried on a few difficult cases. These few mental patients with asthma had been admitted to the St. Francis Hospital, where a large neuropsychiatric department makes many procedures available. Shock therapy, sodium amytal, and hypnosis were all explored.

One young asthmatic girl during hypnosis and with suggestion could be

From the Departments of Allergy and Psychiatry of the Saint Francis Hospital, Pittsburgh, Pennsylvania. This study will be continued by a grant from the Pennsylvania Allergy Society.

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TABLE II. MEDICAL SUMMARY OF FOURTEEN CASES OF BRONCHIAL ASTHMA

Name	Age	Sex	Hosp. Adm.	Etiological Factors										Skin Tests	Immunization	Complications	Follow-up
				Allergy			Infection			Psychic		Others					
				FH	PH	Exam.	Lab.	Hist.	Exam.	Lab.	Hist.	Exam. Imp.					
J.S.	30	M	3	3+	4+	2+	2+	0	2+	1+	2+	3+		NK	Yes	Atelectasis—Postoperative after acute appendicitis	None—"Had been treated years without much help,"
H.M.	68	M	2	1+	2+	2+	3+	2+	2+	3+	3+	4+	Chronic sinusitis	1+	Yes	Emphysema and mediastinal tumor	Died Sept. 1962 self-inflicted gunshot wound
W.B.	29	F	1	0	1+	2+	4+	2+	3+	2+	4+	4+	Chronic sinusitis and tonsillitis	4+	Yes	Malnutrition, mild emphysema	Better Jan. 1952. Moved from Pgh. March 1951
D.R.	39	F	3	0	0	1+	1+	2+	2+	2+	4+	3+		1+	No	Bronchiectasis and emphysema	Mar. 1952 improved. Husband and wife now able to work
R.R.	16	F	3	0	2+	2+	4+	2+	2+	2+	2+	3+		3+	Yes	(?) Emphysema lichenification from atopic dermatitis	Oct. 1950 began immunization was hospitalized didn't continue
E.H.	26	F	4	0	2+	2+	2+	1+	0	0	2+	3+	Glandular imbalance	1+	Yes	Mild obesity, contact dermatitis	Apr. 1951 moved to city reduced and improved
H.H.	36	F	1	0	2+	2+	2+	1+	2+	3+	3+	3+	Chronic sinusitis	1+	Yes	Thrombosed hemorrhoids endocrine dysfunction	Continual immunization much improved
L.A.	35	F	1	2+	2+	2+	1+	0	0	2+	2+	2+		3+	Yes	Mediastinal shift due to collection of gas in splenic flexure	Sept. 1950—Died poorly, immunization stopped
H.A.	27	M	1	NK	0	1+	2+	2+	1+	1+	3+	3+		1+	No	X-ray findings of obstructive emphysema	Admission Sept. 1951. Did not return
C.O.	52	M	3	2+	1+	1+	3+	2+	2+	2+	3+	2+	? Cardiac	2+	Yes	Pulmonary emphysema subcutaneous emphysema	Died Aug. 1951 in status asthmaticus
H.L.	36	F	5	NK	3+	2+	3+	1+	2+	3+	1+	2+	Endocrine imbalance	3+	Yes	(?) Hyperthyroidism	Constant observation but not doing well
H.P.	34	F	2	1+	1+	1+	0	2+	2+	3+	4+	3+	Chronic sinusitis	1+	No	Emphysema spondylitis	Oct. 1950—Last report working
C.L.	20	F	0	4+	4+	2+	2+	2+	1+	3+	1+	1+		4+	Yes		Jan. 1952—Controlled by allergen management
M.L.	26	F	0	3+	4+	2+	3+	2+	2+	2+	2+	2+		4+	Yes		Feb. 1952—Controlled by allergic management

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relieved of her acute attacks. If no asthma was present, it could be induced. Her positive skin tests were not influenced by hypnosis. At the present, hypnosis has been discontinued, because a few patients had great personality changes and they became reliant on the hypnotist for relief. One mental patient with asthma died soon after taking a shock treatment.

All the above led me to believe that a section on psychology should be included in our outline on the etiological study of bronchial asthma (Table I). Certain phases of this chart have been reported in previous papers.^{8,9} The application of projective psychological tests to the study of asthma is not difficult, and the findings in our cases proved interesting.

TABLE I.
THE ETIOLOGICAL DIAGNOSIS OF BRONCHIAL ASTHMA

1. History
 - A. Medical
 - B. Allergy
 - C. Infectious
 - D. Psychological and psychiatric
2. Physical examination
Includes detailed examination of the head, thorax, etc.
3. Laboratory
 - A. Routine
 - a. Urinalysis
 - b. Complete blood count
 - c. Cardiogram
 - d. Basal metabolic rate
 - e. Roentgen examination of chest and sinuses
 1. Fluoroscopy
 2. If shift of mediastinum, do bronchoscopy
 - f. Inspiratory and expiratory films
 - g. Bronchogram
 - B. Allergy
 - a. Nasal smear
 - b. Differential blood count
 - c. Skin tests
 - C. Infectious
 - a. Sedimentation rate
 - b. White blood count
 - c. Bacteriology of sputum
 1. Cells
 2. B. tuberculosis
 - d. Antibiotic susceptibility tests
 - D. Psychologic and psychiatric
 - a. Psychologic questionnaires
 - b. Intelligence tests
 - c. Projective psychological tests
 - d. Psychiatric interview

MEDICAL DISCUSSION OF CASES

The twelve severe cases of asthma studied were all admitted one or more times to a hospital (Table II). All had shortness of breath in recurrent acute or chronic form for several years. Five patients are known to be improved, five did not have sufficient follow-up, and the two oldest patients are dead. The ten living patients are in the young adult age, from sixteen to thirty-nine. After hospital admission, the attacks responded well to aggressive symptomatic therapy. Four of the group had ACTH. Two of the four responded well to this drug and the other two only fair. The symptom-free period after removal of this drug was not lasting. The different etiologic factors of each patient were evaluated quantitatively, but this was difficult. Each showed allergy, infection, and psychic factors to some variable degree. The two so-called controls might be said to have a much higher degree of allergy compared to the twelve severe cases.

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TABLE III. SOCIAL AND PSYCHOLOGICAL SUMMARY

Name	Color	Marital Status	Occupation	Intell. Level	Personality Factors from Test Data			
					Latent Conflict	Manifest Expression	Adjustment	
							Latent	Manifest
J.S.	W	M-C	Clerk for V.A.	Av	Oral aggression and dependency, sexual identification	Submissive, gratification seeking	Anxiety	Dependent
H.M.	W	M-2B	Retired foreman	Av	Hostile but dependent homosexuality	Paranoid defensiveness	Tension and active conflict	Demanding controlling
W.B.	W	M-1G	Housewife	(?)BMD	Schizoid—fearful but aggressive	Withdrawn and repressed	Rage at lack of satisfaction	Passive withdrawal
D.R.	W	2M-1G	Former manager for Isaly's	BMD	Oral dependence and strivings for recognition	Submissive, gratification seeking	Slight tension and conflict	Demanding
R.R.	C	S	Student	Av	Hostile and fearful, masculine strivings	Passive and conforming	Constricted and stereotyped	Dependent
E.H.	W	S	Salesgirl	Av	Oral dependence and strivings for recognition	Repressed ambivalent rationalizing	Rage at lack of satisfaction, anxiety	Confused
H.H.	W	M-3C	Housewife	Av +	Oral dependence and hostility, aggression and fear	Reaction against gratification, seeking sublimation, fantasy	Anxiety	Indecisive mood swings
L.A.	W	M-C	Housewife	Av	Oral dependence	Submissive, gratification seeking	Relatively comfortable	Passive dependent
H.A.	C	S	Circus hand	Av	Oral dependence, sexual identification creative and passive	Homosexuality, paranoid projection	Transitory anxiety	Passive aggression
C.O.	W	M-C	Postoffice janitor	Av +	Oral dependence and need to dominate	Intellectualizing, brief aggressive outbursts	Tension and anxiety	Controlled aggression
H.L.	W	S	Unemployed motor testor	Av	Oral dependence and striving for prestige	Rationalization, evasive, reaction against gratification	Slight anxiety	Passive dependent
H.P.	W	S	Egg candler	MD	Oral dependence and striving for recognition	Repressed, intra-punitive	Anxiety	Passive dependent
C.L.	W	S	Student	S	Oral dependence and independence, rebellion against authority	Reaction against gratification, conforming	Insecure and anxious	Balance between submission and striving
M.L.	W	S	Technician	Av +	Dependence and independence, superego and primitive strivings	Idealistic, repressing, sublimating, fantasizing	Free floating anxiety	Active striving and sublimating

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The two cases which we are using as comparative cases and designating "controls" were moderately severe asthmatic patients without hospital admission or at least recent admission. These two young girls have been studied, managed, and treated by accepted allergy principles and are doing well. They are still taking immunization. No complications appeared in these two controlled cases.

All the cases with hospital admissions showed complications, and nine had some degree of pulmonary emphysema. Nine of the twelve also had had some type of immunization at some time in the past. Among those who had had immunization four were improved. Two with the greatest improvement were among these four; these two are still taking their injection therapy.

TABLE IV. PSYCHOLOGICAL TESTS

Number of Times Each Used			
Intelligence		Personality	
Wechsler-Bellevue	14	Rorschach	14
Stanford Binet	1	Thematic Apperception Tests	6
Goodenough	1	Human Figure Drawing	3
		Bender Visual-Motor Gestalt	2

PSYCHOLOGICAL DISCUSSION OF PATIENTS

A general view of the psychological records of all the patients tested reveals considerable variations of several personality types (Table III). It would be relatively simple to place all these patients under one of the many psychological types of asthmatics described by Abramson.¹ While there appeared to be several diagnostic types, there is abundant evidence of oral conflict; that is, there are strong needs to be dependent, to be nurtured, or to be taken care of. This is a broader dependency than shown by the maternal rejection theory of Miller and Baruch.¹⁰ In contrast to the latent dependent conflicts seen so often, the manifest adjustments of several showed opposed strivings for independence, achievement, self-expression, or aggressiveness. This conflict seems to verify the theories of French and Alexander⁵ wherein the individual unconsciously gets into difficulty by attempting to decide whether or not to leave the dependent situation.

The psychological tests used on all patients were the Wechsler-Bellevue intelligence scale for adolescents and adults and the Rorschach method of personality diagnosis (Table IV). When the intelligence test was scored mental defective, others were used, such as revised Stanford-Binet scale and the Goodenough man drawing test. The Wechsler-Bellevue was preferred because of the interview technique; this often gives incidental information regarding personality characteristics. The anxiety of the anxious asthmatic might in rare cases slightly lower the intelligence score. For this reason we questioned the scoring of one borderline mental defective. It

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was felt that without acute symptoms and language difficulties this patient would score better.

The personality tests all belong to the group known as projective technique. In these, material is presented to the subject which is indefinite in form. Very little direction is given. The subject is allowed freedom in answering as he chooses and in so doing he projects his own ideas, feelings, and ways of reacting into the task. The Rorschach method is based on associations suggested by five black and white and five colored ink blots. The test gives a picture of the patient's intellectual and emotional functioning, particular areas of conflict, and the basic adjustment. The other projective techniques were added to verify the findings of the Rorschach.

Features which seemed to be common to all the records were:

1. Some form of dependency expressed mainly by the oral conflict.
2. Emphasis on intellectual accomplishments and marked strivings for recognition and prestige.
3. Psychosexual immaturity and incomplete acceptance of the rôle in life.
4. The women tend to have masculine identifications and the men lack this identification.

All our personality tests reflect the statement of Goitein:⁶ "Asthma is one of the most primitive of bodily responses."

CASE REPORTS

Case 1.—H. M., aged 68, married and retired. This patient was first seen in the office in July, 1950, with a very complex, extensive medical history. This included "sinus trouble and frequent colds all his life." He had become progressively short of breath since April. The patient was old looking and underweight. The nasal mucosa was swollen and reddened. The breath sounds were harsh, with râles throughout the chest. Blood pressure was 160/94.

A nasal smear showed eosinophils ++, neutrophils +, organisms \pm . The vital capacity was 51 per cent. Skin tests revealed definite reactions to dust, feathers, and several bacterials. X-rays of the chest and sinuses showed involvement of all the sinuses and an irregular shadow below the hilar region in the chest.

Diagnosis: Bronchial asthma

Etiology: 1. Allergy
2. Chronic upper and lower respiratory infection
3. Psychogenic imbalance

Complications: 1. Emphysema
2. Mild hypertension
3. Thoracic mass

The patient did not do well mentally or physically and was finally admitted to the Saint Francis Hospital in a very severe asthmatic attack and in a definitely apprehensive state.

The acute asthmatic attack responded well to symptomatic therapy, including ACTH. The lung shadow in the chest was enlarging and appeared to be malignant. The patient was not considered a good surgical risk. Bronchoscopy was negative.

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During hospitalization the patient was found to be a narcotic addict. He was discharged and was asked to continue his immunization and to have a long series of x-ray treatments over the thoracic mass.

In August, 1951, the patient had lost weight, was apprehensive, and complained of severe bone pain. The asthma was controlled and x-rays of the bones were negative.

He became so difficult to manage at home that he had to be admitted to the Department of Psychiatry. The psychiatric diagnosis was (1) anxiety neurosis, and (2) drug addiction.

During this admission additional x-rays of the chest failed to visualize the former shadow. The patient was in the hospital only a few weeks. Three days after discharge in September, 1951, he was dead of a self-inflicted gunshot wound.

The psychological tests were done while the patient was in the hospital in September, 1950. The negativism, hostility, and paranoid qualities found in the tests suggested that this patient might later commit suicide.

Case 2.—W. B., age 29, married and a Polish G.I. bride. This patient was first seen at the Tuberculosis League Hospital in June, 1949. Her asthma dated from December, 1948, two years after coming to America. She was admitted to the League Hospital for bronchoscopy, and the asthma became very severe after this procedure. This patient had lived in Poland and was relatively healthy when the Russians displaced her into Siberia for three years. She escaped, making her way into the Balkan region, married an American soldier ten years younger, and quickly had a child. She came to America as a "war bride" and lived with her husband's parents. She did poorly at the League Hospital and on July 2, 1949, was transferred to the St. Francis Hospital. She was thought to be a psychogenic asthmatic. Psychiatric consultation did not help, and the patient could not be hypnotized. She responded slowly to symptomatic therapy and when discharged still had a moderate amount of shortness of breath.

The x-rays of the chest showed a shift of the heart to the left which later disappeared. The blood count revealed 12 per cent eosinophils.

After discharge the patient visited her mother in Canada without any help.

In July, 1950, a nasal smear revealed eosinophils + + + + and neutrophils + + + and allergy skin tests showed definite positive reactors.

The patient is now doing well. She started to improve with control of her positive allergens and with immunization. When she moved away from her husband's family and established her own home, improvement was again noted.

Her psychological tests were done as an out-patient in October, 1950. She had the Wechsler-Bellevue, Bender Motor Gestalt, drawings of human figures, Rorschach and thematic apperception tests. There was no question in the psychologist's mind that the apprehension of the patient and her language difficulty influenced her score at least to lower her intelligence scale. The personality test findings verified the impressions of the psychiatrist; in fact, the comparison was striking. The diagnostic impression was a schizoid personality.

The interesting fact in this patient was that the psychological and emotional history overshadowed the definite allergic etiology. The improvement began only when allergic control and immunization was started.

Case 3.—C. O., age 52, married and a post-office janitor. This patient was first seen in the Allergy Clinic about December, 1949. His allergic survey did not reveal many positive skin tests. The initial impression was chronic infectious bronchial asthma with mild to moderate emphysema. Immunization was attempted, but the patient did not do well. He transferred to the office for closer observation but to no

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avail. An acute attack on June 29, 1950, brought him to the hospital. The patient responded well to symptomatic therapy and was discharged July 19, 1950.

The x-ray of the chest showed emphysema. The x-ray of the sinuses revealed chronic bilateral maxillary sinusitis. The blood count showed 10 per cent eosinophils. The patient had a past history of cardiac difficulty, but the cardiogram and heart examinations were negative.

The second admission to the Saint Francis Hospital occurred August 18, 1950. Besides severe asthma, the patient had an acute mediastinal and subcutaneous emphysema. On this admission ACTH was given, and the patient was discharged in fair condition September 6, 1950.

After the second discharge the patient, without consultation, went to State College two hundred miles from Pittsburgh to obtain relief. Here his asthma became very severe and he was admitted to the Bellefonte Hospital. Without any arrangements he was transported by ambulance October 17, 1950, to the Saint Francis Hospital. When he was seen October 19, 1950, he was having severe shortness of breath and was quite hysterical. He signed a release and left the hospital against advice.

He transferred to another physician because he wanted cortisone as an out-patient. He died in an acute asthmatic attack in August, 1951.

The personality tests were given in July, 1950, just before the patient was discharged from the hospital. The findings were most interesting. The Rorschach Tests gave many phallic references. We were at a loss to explain the significance of this. However, the patient's nephew was a physician, and he obtained the following information. The patient's wife suffered from petit mal and when she was coming out of an attack craved sexual satisfaction. The patient no longer could meet her demands. It was after these episodes that the asthma would become severe.

SUMMARY

1. Projective technique should be used by physicians who wish to understand the psychosomatic problems of bronchial asthma. They can be compared to skin tests, a short cut to verify known personality factors and imbalances, and a help to quickly uncover the latent conflicts. Just as positive and negative skin tests sometimes are false, the degree of emotional imbalance necessary for asthma is not constant. Our studies indicate that when improvement is noted the psychic adjustment was not passive dependence but some degree of active striving to meet the life situation. Improvement also seemed to come when the personality imbalance was not fixed but in a state of confusion.

2. The intelligence scales of our patients were about average. Omitting one patient who died, improvement seemed to be associated with better than average intelligence.

3. The Rorschach tests definitely verified much that has been said about the emotional factors in bronchial asthma. When employed, these techniques will give much help. Additional study might indicate that these tests be used to determine what type of psychotherapy should be employed and how the patient might respond. They may also help in prognosis to determine whether the asthmatic attack is temporary or will be sustained.

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ANTIBIOTICS

Relative effectiveness of various antibiotics in local treatment of cutaneous pyogenic infections is given below:

KEY:

A=Aureomycin
B=Bacitracin
C=Chloromycetin

N=Neomycin
P=Polymyxin
T=Terramycin

+ + + Superior
+ + Excellent
+ Satisfactory
+ Inferior
— No Effect

	A	B	C*	N	P	T
Hem. Staph. (Coag. +)	+ + +	+ +	+ + +	+ + + +	—	+ + +
Hem. Strep.	+ + +	+ + +	+ + +	+ + +	—	+ + +
Proteus	?	—	+ + +	+ + +	+	?
Pseudomonas	?	—	?	+ + +	+ + + +	+ + +
Other gram-neg. bacilli	+ +	—	?	+ + +	?	+ + +

*Based on *in vitro* tests.

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RELIEF OF STATUS ASTHMATICUS BY CONTINUOUS INTRAVENOUS ACTH THERAPY

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IN 1849 Thomas Addison¹ first described an anemia which occurred in men when destruction of the adrenal glands occurred. A number of years later he wrote his classic paper in which he described the syndrome which now bears his name.

Shortly thereafter, Secquard in his publication confirmed the fact that the adrenal glands were necessary to life. The monumental work of these men aroused the interest of other investigators (Stewart, Rogoth, Hartman, Abel, and others).

Gradually, the physiologic and metabolic functions of the adrenal glands were investigated by numerous other workers. Adrenocorticotrophic hormone was isolated from the anterior pituitary gland in crude and impure form by J. B. Collip,² E. M. Anderson, and D. S. Thomson in 1933. The chemistry and differentiation of ACTH was also further established.

The development of the adrenal ascorbic acid quantitative bioassay method by Sayers,^{8,9} White, Lewis, Long, and Woodbury further stimulated interest in ACTH. Further work by Sayers and his associates, plus Li^{4,5} and his associates, firmly established that adrenal cortical function occurred under complete pituitary control. As a result of the work of the aforementioned workers, ACTH became available to the medical profession. After ACTH became available for use, Randolph⁷ and Rollins, A. McGehee Harvey and his associates, and B. Rose and his associates reported that patients suffering from chronic intractable asthma and status asthmaticus responded dramatically to ACTH therapy administered via the intramuscular route.

At meetings of the Pennsylvania Allergy Association (Meadville, September, 1950, and Wernersville, May, 1951) and at the Seventh Annual Congress of The American College of Allergists (Chicago, February, 1951), the treatment of status asthmaticus with ACTH via the continuous intravenous method was discussed. This report deals with nineteen patients who have received treatment by the continuous intravenous infusion method with ACTH for the relief of status asthmaticus. We have also treated a number of cases of intractable urticaria, angioneurotic edema,

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TABLE I.

Case No.	Initial Dose of ACTH mg	Duration of I.V. ACTH Treatment	Initial Circulatory Eosinophil Count	Circulatory Eosinophil Count After Treatment
1	80	14 hours	464	6
2	40	12½ hours	508	8
3	40	16 hours	315	0
4	40	13 hours	164	0
5	20	12 hours	776	118
6	20	15½ hours	444	0
7	20	11½ hours	176	0
8	20	14 hours	209	6
9	20	17 hours	916	12
10	20	16 hours	892	0
11	20	18 hours	229	0
12	20	19 hours	92	0
13	20	12 hours	187	4
14	10	15 hours	436	0
15	10	16 hours	—	—
16	20	12½ hours	—	—
17	10	10½ hours	610	0
18	10	14½ hours	22	0
19	20	12½ hours	—	—

periarthritis nodosa, exfoliative dermatitis, and severe drug reactions by the same method. We are not reporting on these cases in this paper.

Dr. R. J. Goodall's and Dr. Leon Unger's method of administering continuous intravenous aminophylline therapy was adapted for administering ACTH via the same route.

METHOD FOR ADMINISTERING CONTINUOUS INTRAVENOUS ACTH THERAPY STATUS ASTHMATICUS

Indications: Hospitalized patients in whom all previous measures have failed.

Amount of ACTH: 20 to 80 mg depending upon severity of symptoms.

Vehicle Used: 1000 cc of 5 per cent glucose in distilled water. Dissolve amount of ACTH to be used in 5 cc of sterile distilled water and add same to the bottle containing the 1000 cc of 5 per cent glucose in distilled water. To same bottle add 10 cc of sterile solution of potassium chloride, 20 mEq of potassium as potassium chloride. The administration of potassium salts must be carried out with caution in order to avoid excessive plasma concentrations with resultant potassium intoxication.

Use of vehicle: The 1000 cc of 5 per cent glucose in distilled water containing from 20 to 80 mg of ACTH (use large dose only if patient is in extreme and severe status) plus 20 mEq of potassium chloride, is then administered by continuous intravenous infusion.

Rate of Flow: 28 drops per minute, one liter in twelve hours.

Equipment: (a) 22 gauge, short bevel, 1½-inch needle. (b) 20 to 80 mg ACTH dissolved in 5 cc of distilled water. (c) One sterile ampule of potassium chloride, 20 mEq. (d) 10-cc syringe plus one 22-gauge, 1¼-inch needle. (e) Rubber tubing with clamp. (f) Liter flasks. (g) Padded splint for forearm.

Site of Injection: Broad volar and dorsal surface of forearm. Avoid joints.

Precautions: (a) Flask must not run dry. (b) If vein becomes inflamed, transfer to another vein. (c) Tarail and Elkinton¹⁰ recommend that the rate of administration be controlled so as not to exceed 20 mEq of potassium per hour. They quote the work of Darrow, who estimates that 3.5 mEq per kg of body weight per day may be given safely in a period of four to eight hours.

Toxic Effects: None observed.

Duration of Treatment: Average—one to three days in status asthmaticus.

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Results: This method of therapy in our hands has produced excellent results. The stimulation that the patient receives from continuous ACTH therapy usually produces complete relaxation within a period of twenty-four hours. It is only necessary to give this form of therapy for a period of from twenty-four to seventy-two hours. If the clinical effects of adrenal overstimulation should occur, the effects are readily reversed upon lowered or discontinued therapy. Patients treated so far have not developed edema. They are placed on a low-salt diet. With this form of therapy they receive additional potassium intravenously. Daily weight charts should be kept as a guide to abnormal weight gain. Muscle weakness, fatigue, or paresthesias reflect potassium deficiency. I have not observed these symptoms in patients treated so far.

The following laboratory studies were carried out on each patient that received continuous ACTH therapy:

- Complete blood count
- Sedimentation rate studies
- Complete urinalysis
- Pre-treatment circulatory eosinophil count
- Post-treatment circulatory eosinophil count.

Circulatory eosinophil counts were also done during and after each course of continuous intravenous ACTH treatment.⁷ Specimens of the patients' urine were examined for sugar each day of continuous intravenous ACTH treatment, and after the completion of treatment. The patients studied were all hospitalized. Ten of the patients were placed on low-salt diets. Nine of the patients were not allowed to add salt to their food as it was served from the diet kitchen. Potassium chloride was administered intravenously in conjunction with the ACTH.¹⁰ Pituitary adrenocorticotrophic hormone was administered only by the continuous intravenous route. Treatment usually started after the patient had his breakfast and continued until approximately 8:00 or 10:00 p.m. On a number of occasions it was necessary to continue the therapy throughout the night.

The first patient to receive treatment with ACTH by means of the continuous intravenous method was a forty-six-year-old white man, suffering from extremely severe status asthmaticus of five days' duration. In June, 1950, he was hospitalized and received aminophylline intravenously, 1:500 epinephrine in gelatin intramuscularly, 5 per cent glucose in normal saline intravenously, sodium iodide intravenously, potassium iodide and ammonium chloride orally, and numerous injections of 1:100 epinephrine hydrochloride subcutaneously. He also received aminophylline via the continuous intravenous infusion method.³ He experienced no clinical improvement. His condition became worse with each passing day. His family was consulted concerning the advisability of giving him ACTH via the continuous intravenous route. Permission was obtained from both him and his family to proceed with the therapy.

Over a fourteen-hour period of time he received 80 mg of Acthar* in-

*Manufactured by Armour Laboratories, Chicago.

travenously. His improvement was dramatic. His circulatory eosinophil count dropped from 464 to 6. The last count was done approximately twenty-two hours after the first. He improved for three days and then suffered a relapse. His response to an additional 40 mg of ACTH via the continuous intravenous route was again dramatic. Five days later it was necessary to give him a third course of therapy via the same route. This time he received only 20 mg of ACTH. His symptoms again subsided, and his recovery was uneventful. He was discharged on the twelfth day after his admission to the hospital and stayed asthma-free for six weeks, at which time he developed an acute respiratory tract infection that acted as a trigger mechanism, again precipitating his attacks of asthma. He was, however, able to control these attacks by using Isuprel hydrochloride sublingually and 1:100 epinephrine chloride via the oral inhalation route.

The next patient to receive treatment was J. B., a fifty-year-old white woman. She was admitted to the hospital suffering from status asthmaticus of seasonal origin. She had been studied by several competent allergists. She had received specific hyposensitization therapy for three years with antigens prepared from the fall pollens, early summer grass pollens, and epidermals to which she was sensitive. She also had practiced environmental control and avoided those foods to which she knew she was clinically sensitive.

She was hospitalized for forty-eight hours before she received continuous intravenous ACTH therapy. During this preliminary period of hospitalization she received aminophylline intravenously, oxygen by mask, adrenalin in oil, sedation, and fluids by hypodermic. She experienced some slight relief. Continuous intravenous ACTH therapy was started on the third day after her admission. She received 40 mg of ACTH over a twelve and one half-hour period of time. On the following day she was given 20 mg of ACTH by the same method over a period of eleven hours. The drop in her circulatory eosinophil count and sedimentation rate time was dramatic. She improved and required no further continuous cortical stimulation.

Five cases of status asthmaticus were treated during the next three weeks with ACTH administered via the continuous intravenous drip method. Two of these patients received two 40-mg courses of ACTH intravenous treatment administered over a three-day period of time. Enough adrenal cortical stimulation was obtained in the last three patients from the administration of 20 mg of ACTH by the continuous intravenous method to bring about a complete alleviation of their symptoms. This was further evidenced by the fall in their circulatory eosinophil counts.

The next three patients treated revealed that the duration of time of administration was also of great importance. Adrenal cortical activity seems to persist for approximately twice the time that it takes to administer the ACTH via the continuous drip method. To illustrate: if it

takes twelve hours to administer the therapy, improvement will take place in the patient for a period of from twenty-four to thirty hours. We were further able to establish that it is not necessary to give large doses of ACTH to stimulate adrenal cortical activity when it is given by the continuous intravenous infusion method.

According to Selye there is a phenomenon which occurs when a human being is exposed to stress: the alarm reaction. It appears in conjunction with stress of all types, including fear, anger, trauma, mental stress, emotional stress, stress due to disease, et cetera. The alarm reaction results from stimulation of the adrenal medulla by the so-called parasympathetic nervous system. When the adrenal medulla is stimulated it secretes large quantities of epinephrine. When the human reacts acutely to a situation of stress, he becomes more alert. The carbohydrate reserves in the body are mobilized from the liver, spleen, and so forth. Glycogen stored in the muscles is mobilized. Muscular strength is increased. At the same time the pupils dilate. The peripheral blood vessels contract. The contraction of the peripheral blood vessels, in turn, provides better cerebral circulation. Perspiration occurs because of the sudden mobilization of energy which requires the loss of more heat by the body.

These physiological stress changes take place in variable degrees when a human reacts to stress. Needless to say, the events mentioned cannot go on indefinitely, as the body energy reserves will be completely depleted. Body energy reserves must, therefore, be replenished. Replenishment of the body reserves occurs by stimulation of the pituitary gland, which, in turn, puts out ACTH, which stimulates the adrenal cortex to produce adrenocortical hormones. The adrenocorticoids aid in balancing the alarm reaction. Body energy is replenished and replaced. The replacing of the body energy, in turn, makes it possible for the human to continue to react to prolonged stress.

It is known that an increase in the excretion of the following chemicals takes place under maximum adrenocortical stimulation: nitrogen, potassium, phosphate, and calcium. Loss of these substances does not occur under minimum adrenocortical stimulation.

To date we have not seen one case of renal glycosuria following the administration of ACTH by the continuous intravenous infusion method. Neither have we seen a case of edema resulting after the administration of ACTH by this method. The good results that we have obtained are probably due to the following:

1. Patients are carefully screened.
2. Small doses of ACTH are administered.
3. Potassium is administered concomitantly.
4. The patient is placed on a low-salt diet during the period that the ACTH is being administered.
5. The stimulation of the adrenal gland takes place gradually.

6. The stimulation of the adrenal cortex is gradual, which, in turn, gives rise to the gradual production of the adrenocortical hormones.
7. Body energy is replenished and replaced.

The eleventh patient, a man, aged fifty-two, was admitted suffering from extreme and severe status asthmaticus, plus dehydration and loss of weight. All previous measures had failed to relieve his attacks of asthma. After the completion of his initial laboratory tests, he was given 20 mg of ACTH via the continuous intravenous method over a period of fourteen hours. His response was satisfactory. Twenty-six hours after admission he again became dyspneic and received additional treatment with 20 mg of ACTH by infusion. His response was good. He was fairly comfortable for thirty-one hours, at which time it was necessary to give him a third course of intravenous ACTH therapy, 20 mg. After receiving the third course he stayed symptom-free for four days. His appetite, weight, and general condition improved during the time he was receiving the three courses of continuous intravenous ACTH. His electrocardiographic studies were all normal. He has since developed attacks of asthma, which, however, were easily controlled by conventional means.

By clinical trial and observation it became evident that it was not necessary to give large doses of ACTH to obtain a favorable result when it was administered via the continuous intravenous infusion method. From then on the dose of ACTH administered was reduced to 20 mg. Further experience taught us that in some cases 10 mg of ACTH produced sufficient continuous cortical stimulation when given by the continuous intravenous infusion method to bring about a reversal of symptoms in status asthmaticus. None of the last eight patients received more than 20 mg of ACTH at any one administration via the continuous intravenous infusion method. It also became evident that the longer the time of administration the greater the duration of response. Therefore, we tried to lengthen the time of administration by reducing the rate of flow of the solution containing the ACTH. It was further observed that it was not necessary to repeat the infusion as often if the duration of time of administration was lengthened. These facts are extremely important.

CONCLUSIONS

1. Only small amounts of ACTH are required to produce continued adrenal cortical stimulation.
2. The stimulation persists for a considerable period of time after treatment is discontinued.
3. Stimulation of adrenal cortical activity can again be easily established when additional treatment is needed.
4. The cost of treatment of the patient is reduced.
5. Treatment can be easily administered to a hospitalized patient.

STATUS ASTHMATICUS—LOCKEY ET AL

6. The amount of adrenal stimulation obtained by continuous intravenous ACTH treatment in many cases is sufficient to bring about a complete reversal of the status asthmaticus from which the patient is suffering.

7. No cases of anaphylaxis have been encountered to date. Precautions should be taken to ascertain whether or not it may occur, and to counteract it if it should occur.

8. The possible toxic and remote effects that may occur from continuous intravenous ACTH treatment should always be kept in mind.

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POLIOMYELITIS

Publicity given the supposed relationship between hypodermic injections and the incidence and severity of polio has caused considerable concern among parents. Cioffari reviewed the histories of 1,601 private patients who received a total of 3,200 routine immunizing injections during a four-year period. Only one case of mild paralytic polio developed in this group. From this and other observations it is concluded that "... there is no relationship between an injection and the inciting of poliomyelitis ..." and that "... immunization against communicable diseases should be carried out the year round."—Cioffari, M.S.: Poliomyelitis and injections. *J. Michigan M.S.*, 51:727, 1952.

SEASONAL ALLERGIC IRITIS

Case Report

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ACUTE iritis has been studied by many investigators.^{6,10,11,14,18,19,20,21,23,25,26} Gifford,⁸ in a review of the literature in 1931, said that as a result of the work of the past twenty years, it was evident that instead of too few etiologic possibilities, there were now too many. Allergic Iritis was found to be due to extrinsic allergens such as pollens, dusts, inhalants, foods, and epidermals.

The production of inflammation in parts of the eye other than the iris, due to extrinsic allergens, is fairly well accepted. Mauksch¹⁵ reported a case of superficial keratitis due to pollen allergy. Annenberg¹ reported marked corneal reactions due to the cutting of pigweeds pollinating heavily in September in Iowa. Allergic involvement of the conjunctivae during the hay fever season is well known. Many allergists have discussed the etiology of subacute and chronic forms of conjunctival inflammation, described by Lehrfeld¹³ which begins characteristically in the late spring or early summer and persists as long as the warm weather lasts, and is thus called vernal conjunctivitis. The subject of ocular allergy involving all parts of the eye has been completely discussed by Woods.²⁴

One of the earliest cases of seasonal iritis was reported by Benedict,³ at the Mayo Clinic in 1920. The patient had severe iritis which recurred every spring and fall for a period of six years. This was attributed to foci of infection in a tooth. Hurwitz⁹ reported a case of hay fever with typical itching of the eyes for several years. This patient developed acute iritis just prior to the hay fever season on two successive years. Parry¹⁶ reported two cases of acute iritis resulting from what he thought was allergy to eggs. Bothman^{4,5} reported several cases due to pollens, molds, house dust, and foods. Rappaport,¹⁷ in a discussion of Bothman's paper, brought out the fact that these cases were usually unilateral and admitted frankly that he did not know why the iritis occurred.

Woods²⁴ classifies endogenous uveitis, as seen in Table I. In the gran-

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Doctor Fein is an Associate Fellow of The American College of Allergists.

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ulomatous group are those conditions which cause granulomatous types of inflammations. The nongranulomatous uveitis tends to affect primarily the anterior uveal tract, and consists of bacterial hypersensitivities due to streptococci, gonococci, and foci of infection. Endophthalmitis phaco-Anaphylaxis is considered a part of this group. In this classification there is grouped a number of types of uveitis of unknown etiology. The classification does not include nonbacterial allergens.

TABLE I. CLASSIFICATION OF ENDOGENOUS UVEITIS

TYPES	
A. Granulomatous Uveitis (Tends to Affect the Entire Uveal Tract)	
1.	Syphilis
2.	Tuberculosis
3.	Brucellosis
4.	Sarcoidosis
5.	Toxoplasmosis
6.	Virus Diseases
7.	Rare Causes
	A. Leprosy
	B. Histoplasmosis
B. Nongranulomatous Uveitis (Tends to Affect Primarily the Anterior Uveal Tract)	
1.	Bacterial Hypersensitivity
	A. Streptococci
	B. Gonococci
	C. Foci of Infection
2.	Endophthalmitis Phaco-Anaphylaxis
3.	Uveitis of Unknown Etiology

*Woods, A.C.

CASE REPORT

Mr. A. B., a thirty-five-year-old white male, was first seen by one of us on April 4, 1949. His chief complaint was pain in the right eye which had been present for fifteen days. At that time he gave a history of recurrent iritis in the right eye in the fall of each year since 1940 (Table III). In March, 1948, he had had acute iritis during the spring. The patient stated that his present trouble started on March 21, 1949, with pain and redness in the right eye. After a period of one week he had to discontinue work, since the boric acid compresses which he had been using gave no relief.

Past Medical History.—In 1943, he sustained a fracture of three vertebrae and was hospitalized for a period of three months.

Allergic History.—There was no family history of allergy. He had not had hay fever, asthma, childhood eczema, or food intolerances.

Special Systems.—There was no apparent history of foci of infection of the sinuses, genitourinary tract, or gastrointestinal tract.

Physical Examination.—The only positive findings were in the right eye.

Ophthalmoscopic Examination.—Tension in both eyes was normal. Pupillary reaction: The right eye was dilated by atropine to 5 mm. The left eye was normal. External examination: ciliary injection present in the right, normal in the left. There was one small posterior synechia in the right. There was a mild beam in the anterior chamber. The suspended particles were relatively coarse, and thermal convection currents were easily demonstrated. No keratic precipitates were present; the media and fundus appeared clear.

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Nose and throat, dental, genitourinary, gastrointestinal, and arthritic surveys revealed no foci of infection. The remainder of the physical examination was otherwise essentially negative.

TABLE II. LABORATORY PROCEDURES DONE IN DIFFERENTIAL DIAGNOSIS OF UVEITIS

TEST	REACTION
A. Granulomatous Uveitis	
Blood Wasserman.	Negative
Mantoux Test (P.P.D. 1st, 2nd, and 3rd Strength).	Negative
Brucellosis Skin Test (Brucellerogen 0.1 C.C.).	Negative
Agglutination Test	
Brucella Abortus.	Negative
Brucella Melitensis.	Negative
Sacroidosis Skin Test (Nickerson-Kveim) (Spleen Extract 0.15 C.C.).	Negative
Toxoplasmosis Skin Test (Frenkel) (Toxoplasmin 0.1 C.C.).	Negative
Histoplasmosis Skin Test (Histoplasmin 1-1000, 0.1 C.C.).	3 +
B. Nongranulomatous Uveitis	
1. Bacterial Hypersensitivity	
A. Streptococcus Skin Test (Group A 1-10, 0.1 C.C.).	Negative
B. Gonococcus Skin Test (Vaccine 1-100, 0.1 C.C.).	Negative
C. Staphylococcus Skin Test (Toxin 1-100, 0.1 C.C.).	Negative
2. Endophthalmitis Phaco-Anaphylaxis (Not done)	
3. Uveitis of Unknown Etiology	
Allergy Skin Tests.—	
Inhalants.—	
Mixed Ragweeds, .001.	Marked
Mixed Grasses, .001.	Marked
Mixed Trees, .001.	Marked
Mesquite, .001.	Marked
Ligustrum, .001.	Marked
Kapok, .001.	Marked
House Dust, Conc.	Moderate
Feathers, .1	Moderate
Food Extracts.—	
Beef, Rye, Corn, 1-10.	Moderate
Egg White, .001, Milk-10, Wheat 1-10	Mild

Laboratory Procedures.—The urine was negative for albumin and sugar. The blood showed a red blood count of 4,250,000, hemoglobin 85 per cent. The white blood count was 6,000 with a differential count of 48 neutrophils, 32 lymphocytes, 13 monocytes, 6 eosinophils, and 1 basophil. Sedimentation rate (Modified Cutler) was 20 mm per hour. The N.P.N. was 35.4 mg per cent. Total protein was 5.8 gm per cent, serum albumin 3.8 gm per cent, and serum globulin 2.0 gm per cent. Nasal smears for eosinophils were negative. Concentrated smears of the sputum for acid-fast bacilli were reported as negative. Prostatic and conjunctival secretions examined showed no organisms or eosinophils.

X-Rays.—Chest—The heart and great vessels appeared normal. There were no abnormal hilar calcifications noted. Teeth—negative. Nasal accessory sinuses—the frontal sinuses appeared small. Gastrointestinal series—negative. Barium enema—negative.

Electrocardiogram.—Within normal limits.

Special Tests.—Table II. Granulomatous iritis^{2,7,12,22} was ruled out.

Tests for bacterial hypersensitivities were negative. By intradermal skin tests, the patient showed marked reactions to mixed ragweeds, mixed grasses, mixed trees, mesquite, ligustrum (privet), and kapok. He showed moderate reactions to house dust, feathers, beef, rye, and corn. There were mild reactions to egg white, milk, and wheat.

Treatment.—The patient was given atropine sulfate to be instilled into the conjunctival sac three times a day. Intramuscular penicillin, 300,000 units, and streptomycin hydrochloride, 0.5 gm, were injected twice daily. He received sulfadiazine, 0.5 gm, every four hours for three days orally.

SEASONAL ALLERGIC IRITIS—FEIN AND SWINNY

TABLE III. SEASONAL OCCURENCE OF IRITIS

DATE	DIAGNOSIS	LOCATION	DURATION	TREATMENT
Sept. 22, 1940	Iritis, Acute, Right, Moderate	Station Hospital, Ft. Sam Houston, Texas	Hospital 8 Days	Mydriatics Fever Therapy (Typhoid Vaccine)
Nov. 5, 1941	Iritis, Acute, Right, Severe	Station Hospital, Ft. Sam Houston, Texas	Hospital 28 Days	Mydriatics Tooth Extraction
Oct. 15, 1942	Iritis, Acute, Right, Mild	Eye Clinic, Station Hospital, Ft. Sam Houston, Texas	Out-Patient 10 Days	Mydriatics
Nov. 2, 1943	Iritis, Acute, Right, Mild	Family Physician, San Antonio, Texas	Home 6 Days	Mydriatics Boric Acid Compresses
Nov. 12, 1944	Iritis, Acute, Right, Mild	Eye Clinic, V. A. Regional Office, San Antonio, Texas	Out-Patient 8 Days	Mydriatics
Nov. 4, 1945	Iritis, Acute, Right, Mild	San Antonio, Texas	Home 3 Days	Self Medication Atropine Sulfate
Nov. 11, 1946	Iritis, Acute, Right, Moderate	Family Physician, San Antonio, Texas	Home 20 Days	Atropine Sulfate
Oct. 20, 1947	Iritis, Acute, Right, Mild	San Antonio, Texas	Home 13 Days	Self Medication Atropine Sulfate
Mar. 22, 1948	Iritis, Acute, Right, Moderate Possibly Due To Allergy	Brooke Army Hospital, Ft. Sam Houston, Texas	Hospital 33 Days	Mydriatics Fever Therapy (Typhoid Vaccine)
March 21, 1949	Iritis, Acute, Right, Moderate Due to Allergy Specific Allergen Undetermined	Brooke General Hospital Ft. Sam Houston, Texas	Hospital 17 Days	Mydriatics Antibiotics Hyposensitization
June 11, 1951	Iritis, Acute, Right, Severe Allergic	Allergy Clinic, V. A. Regional Office San Antonio, Texas	Out-Patient 2 Days	Cortisone Acetate Hyposensitization

Course.—Table III. The eye improved slowly. As soon as the acute iritis subsided, the patient was started on a series of desensitization injections since the seasonal occurrence of the patient's eye symptoms was strongly suggestive of allergy. He was hypsensitized to house dust and the prevalent pollens on May 5, 1949, and given biweekly treatments from that date until October 1, 1950, or a period of nineteen months. It is seen that he had no iritis in the spring or fall of 1950. This was the first time that he had had no iritis in the past ten years.

On June 11, 1951, the patient was seen at the Allergy Clinic, V.A. Regional Office, San Antonio, Texas, with an inflamed, painful right eye. Because of the acuteness of the iritis, he was referred to the Eye Clinic. The ophthalmologist started the patient on cortisone acetate suspension, two drops every hour during the day, and every two hours during the night for a period of two days. He recommended that intradermal skin tests be done, and desensitization treatment be given in view of his past history. On intradermal testing, he was found to be markedly sensitive to mixed ragweeds, mixed grasses, mixed trees, mesquite, and kapok. There was a moderate reaction to house dust, feathers, amaranth, and molds, and a mild reaction to orange, white potato, and egg white.

Desensitization was initiated after the acute iritis subsided, and there has been no spring or summer iritis to this date. The last ophthalmic examination was done on March 15, 1952, and showed the eye to be normal.

DISCUSSION

This case report presents a detailed history of events of a patient with a seasonal occurrence of iritis. Most cases previously reported did not show this seasonal relationship. Bothman's^{4,5} cases showed recurrences of iritis which ran from seven to fourteen years. He attributed these attacks of iritis to house dust, feathers, molds, and certain foods. There was little

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or no correlation made to the seasonal variations of the attacks. All of these individuals were found to be highly allergic.

It is seen (Table III) that the occurrence of iritis corresponded to the fall for the first eight years, during which time the ragweed pollens were the most prevalent. The most prevalent spring pollens during the time the iritis occurred were those of the trees and grasses. It was seen in our case, and in others, that despite the absence of foci, and the elimination of those foci present, the patients continued to have attacks of iritis for years after elimination.

Following the first period of desensitization for nineteen months by one of us, it was seen that there was no recurrence of iritis in the right eye during the season in which it had occurred in the past. The last episode of iritis, which is shown in Table III, occurred on June 11, 1951, following a period of eight months in which no desensitization treatment had been received. This episode was the first to occur in the summer months and was at the height of the grass season, a pollen to which the patient showed a marked sensitivity.

We have attempted to eliminate all of the possibilities that this case might be considered as one of the granulomatous group by the series of laboratory procedures and skin tests^{2,7,12,22} described in Table II. We have decided that from the evidence presented in this case, iritis can be caused by pollen and can occur seasonally due to a marked sensitivity to the prevalent, nonbacterial airborne pollens.

It is seen that the addition of cortisone acetate in the treatment of iritis is well established, and by using this treatment in the last episode, there was a shortening of the attack to approximately forty-eight hours. The shortest previous attack was in November, 1945, which lasted for three days.

It is hoped that this case has added to the evidence reported in the past that allergy not only plays an important role in the etiology of iritis but is a definite etiological factor in nongranulomatous iritis.

SUMMARY

1. A case of seasonal allergic iritis occurring in one eye over a period of twelve years is presented.
2. The literature, classification, and differential diagnosis is discussed.
3. The results of treatment by cortisone acetate suspension and desensitization with nonbacterial airborne pollens is reported.
4. The case reported shows that nonbacterial airborne allergens must be considered as an etiologic factor in the production of iritis of unknown etiology.

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BOTANICAL SURVEY OF NORTHERN CALIFORNIA

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NORTHERN California lies between latitudes 42° north and 35° south, being approximately 480 miles long and 210 miles wide. The Coast Range, varying between 1,500 and 6,000 feet extends along the Pacific Ocean. From Oregon the Cascades descend into Eastern California about 150 miles; Mount Shasta rising 14,162 feet and Mount Lassen, 10,453 feet, are in this area. The Sierra Nevadas extend 300 miles south along the eastern border of California, attaining heights of 12,000 to 14,500 feet. In the north-central area the Coast Range and the Cascades join. The Tehachepi Mountains unite the two lateral ranges in the south. Along the coastal area there are various small and large valleys, canyons and low-lying hills.

San Francisco Bay is in the center of Northern California, and into it the Sacramento River from the north and the San Joaquin River from the south empty. San Francisco and Oakland and their adjoining cities are on this bay. Between the two large mountain ranges, the Sacramento Valley in the north and the San Joaquin Valley in the south lies the great Central Valley of California. The east slopes of the Sierras and the Cascades extend down into the desert areas of Nevada.

In the coastal area rain is abundant in the north and scanty in the south, with much fog through the spring and summer months. Freezing temperatures are rare. Rain is much heavier in the Sacramento than in the southern San Joaquin Valley. Freezing temperatures occur throughout the Central Valley, and from June until October high temperatures frequently are present. In the winter the eastern mountains and the northern coast range and, at times, the Tehachepis are covered with snow. The rivers from the western slope of the Sierras, carrying the melted snows, bring important water for irrigation in the Central Valley.

Agriculture is the important industry in Northern California, even in the San Francisco Bay area. In these areas, moreover, are the financial, industrial and cultural centers of Northern California. Lumbering is of great importance, and mining and fishing are of lesser importance in the mountain areas and on the seacoast.

According to their importance, the pollen-producing plants of Northern California are listed in Table 1. The degree, frequency and months of pollination, as well as comments on each genus or species, are detailed in each of the three designated areas. The publications of various botanists and the advice especially of Professor H. E. McMinn, along with the observations of the present writer during a thirty-five year period, have yielded this information.

BOTANICAL SURVEY—ROWE

TABLE I. BOTANICAL SURVEY OF NORTHERN CALIFORNIA
3—Abundant; 2—Common; 1—Scarce
Pollination: 1 Moderate V Maximum

Trees (Some Shrubs and Vines)	Months of Pollination												Coastal Area	Central Valley	East Sierra	Occurrence and Distribution
	1	2	3	4	5	6	7	8	9	10	11	12				
Aceraceae																
Acer Macrophyllum—Big Leaf Maple	✓	✓	✓	✓	✓	✓	✓	✓					2	2	2	Native; along streams; streets, parks, and garden
Acer Negundo and vars.—Box Elder													2	2	2	Native and introduced; extensively planted
Acer Saccharinum and vars.—Silver Maple													2	2	2	Introduced; garden and park tree
Anacardiaceae																
Azadirachta indica—California Pepper Tree					✓	✓	✓	✓					2	2		Introduced; extensively planted in warmer areas
Burseraceae																
Alnus Rhombifolia—White Alder	1	✓	✓	✓	✓	✓	✓	✓					3	3		Native; Coast range valleys, Great Valley, western slope of Sierra Nevada
Alnus																
Alnus Rubia—Red Alder	1	✓	✓	✓	✓	✓	✓	✓					2	2	2	Native; Coastal Stream Banks
Alnus sps.—Alder	1	✓	✓	✓	✓	✓	✓	✓					3	3	3	North Coast and high mountain meadows in the Sierras
Betula sps.—Birch	1	✓	✓	✓	✓	✓	✓	✓					3	3	3	Introduced and native; street, parks, and gardens
Corylus sps.—Hazelnut	1	✓	✓	✓	✓	✓	✓	✓					2	2	2	Introduced; cultivated as filberts; native along streams and most wooded canyons
Cypripediaceae																
Chamaecyparis Lawsoniana—Lawson Cypress	1	1	1	✓	✓	✓	✓	✓	1	1	1	1	1	1	1	Native; parks and gardens
Cupressus sps.—Cypress	1	1	1	✓	✓	✓	✓	✓	1	1	1	1	1	1	1	Introduced and native; park and lawn trees
Juniperus sps.—Juniper	1	1	1	✓	✓	✓	✓	✓					1	1	1	Introduced and native; garden trees and shrubs
Libocedrus decurrens—Incense Cedar	1	1	1	✓	✓	✓	✓	✓					1	1	1	Native to mountains; park and garden trees
Thuja plicata—Giant Arborvitae—Canoe Cedar	1	1	1	✓	✓	✓	✓	✓					2	1	1	Native to north coast; park and garden trees
Thuja sps.—Arborvitae	✓	✓	✓	✓	✓	✓	✓	✓					1	1	1	Introduced; parks and gardens
Fagaceae																
Castanea sps.—Chestnut									1	✓	✓	✓	1	1	1	Introduced; occasionally in parks and gardens
Castanopsis sp.—Chinquapin									1	✓	✓	✓	1	1	1	Native—in mountain areas—scattered. Pollen is heavy
Fagus sps.—Beech									1	✓	✓	✓	1	1	1	Introduced; occasionally planted in parks and gardens
Lithocarpus densiflora—Tan Oak									1	✓	✓	✓	1	1	1	Native; Coast Ranges and western slope of Sierra Nevada
Quercus agrifolia—Coast Live Oak									1	✓	✓	✓	3	2	2	Native; park and garden trees
Quercus chrysolepis—Canyon Oak									1	✓	✓	✓	2	2	2	Native to mountain canyons
Quercus Douglasii—Blue Oak									1	✓	✓	✓	2	2	2	Native; lower dry mountain slopes of middle and inner Coast Range and western slope of Sierra Nevada
Quercus dumosa—Scrub Oak									1	✓	✓	✓	2	2	2	Native; dry mountain slopes of inner Coast Range and western slope of Sierra Nevada
Quercus																
Quercus Garryana—Oregon Oak													2	3		Native north coast, east to northern Sierra Nevada
Quercus lobata—Valley Oak													3	3	3	Native; mostly in the Great Valley and adjacent foothill valleys
Quercus wislizeni—Interior Live Oak													3	3		Native; lower mountain slopes and foothills
Garryaceae																
Garrya sps.—Silk Tassel Bush	✓	✓	✓	✓	✓	✓	✓	✓				✓	1	1	1	Native; 4 species of mountains and foothill areas; occasionally cultivated
Guttiferaceae																
Caraya pecan—Pecan													1	1		Introduced; occasionally cultivated
Juglans californica—California Black Walnut													3	3		Native in warmer valleys about old Indian habitations, often cultivated
Juglans																
Juglans regia—English Walnut													2	2	1	Introduced; cultivated in orchards and as shade trees
Juglans nigra—Eastern Black Walnut													1	1	1	Introduced; occasionally cultivated

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[illegible]

TABLE I. BOTANICAL SURVEY OF NORTHERN CALIFORNIA—CONT.

3—Abundant; 2—Common; 1—Scarce

Trees (Some Shrubs and Vines)													Months of Pollination												Coast-land Area	Central Valley	East Sierra	Occurrence and Distribution																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
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TABLE I. BOTANICAL SURVEY OF NORTHERN CALIFORNIA—CONT.
3—Abundant; 2—Common; 1—Scarce

Woods—Continued	Months of Pollination												Coastal Area	Central Valley	East Sierra	Occurrence and Distribution
	1	2	3	4	5	6	7	8	9	10	11	12				
Chenopodium ambrosioides—Mexican Tea													2	2	2	Introduced; widely scattered in waste places
Chenopodium anthelminticum—Wormseed													3	2	2	Introduced; very closely related to Chenopodium ambrosioides
Chenopodium murale—Nettleleaf, Goosefoot, Sowbane													3	2	2	Introduced; common weed in cultivated fields
Salicornia sps.—Pickweed													1	2	3	Salt marshes along the coast and inland alkaline marshes and flats
Salsola Kali var. tenuifolia—Russian Thistle													1	2	3	Introduced; common weed in cultivated fields, especially in Eastern Sierra
Sarcobatus vermiculatus—Black Greasewood													1	1	3	Native; alkaline soils of desert valleys
Suaeda sps.—Alkali Blite													1	1	1	Native; salt marshes and alkali flats
Compositae																
Ambrosia (Ragweed Tribe)													1	3	2	Native; widespread along roadsides, railroad rights-of-way and wastelands, mostly in valleys
Ambrosia psilostachya—Western Ragweed													1	3	2	Native; widespread along roadsides, railroad rights-of-way and wastelands, mostly in valleys
Franseria acanthiophora—Fades Ragweed													3	3		Native; sandy shores from Lower California to British Columbia
Franseria bipinnatifida—Beach or Sand Bur													2			Native; sandy shores from Lower California to Washington
Franseria chamoensis—Beach or Sand Bur													2			Native; common on Mojave and Colorado desert
Franseria dumosa—Burro Weed													1	1	2	Native; occasional importance
Iva axillaris—Poverty Weed													2	2	2	Introduced; in moist waste places
Xanthium canadense—Cocklebur													2	2	2	Introduced; neglected fields and barnyards
Xanthium spinosum—Spiny Clothbur													2	2		Introduced; neglected fields and barnyards
Cruciferae																
Brassica sps.—Mustard													1	1	1	Common introduced weeds of cultivated lands and waste places
Leg.													1	1	1	Cultivated and often escaped
Medicago sativa—Alfalfa													1	1	1	Introduced; naturalized throughout California. Planted as a forage plant
Melilotus sps.—Sweet Clover													1	1	1	Introduced; common weed in waste places, on lawns, golf courses, etc.; throughout the state
Plantaginaceae													3	3	2	Introduced; common weed in waste places, on lawns, golf courses, etc.; throughout the state
Plantago lanceolata—English Plantain													2	2	2	Introduced; common weed in waste places, on lawns, golf courses, etc.; throughout the state
Plantago major—Common Plantain													2	2	2	Introduced; common weed in waste places, on lawns, golf courses, etc.; throughout the state
Polygonaceae													3	3	2	Introduced; common weed throughout the area
Rumex acetosella—Sheep Sorrel													2	2	2	Introduced; weed of moist lands in the valleys and to middle elevations in the mountains
Rumex conglomeratus—Green Dock													2	2	2	Introduced; common weed on low neglected land
Rumex crispus—Curly Dock													2	2	2	Introduced; common weed of moist waste places
Rumex pulcher—Fiddle Dock													2	2	2	Introduced; common weed of moist waste places
Urticaceae													2	2	2	Native; lowlands near coast
Urtica californica—Coast Nettle													2	2	2	Native; lowlands near coast
Urtica gracilis var. holosericea—Creek Nettle													2	2	2	Native; common along creeks and other wet places throughout the area
Anthemideae (Mayweed Tribe)													2	2	2	Occasional in few scattered localities
Artemisia biennis—Biennial Wormwood													2	2	2	Native Shrub; San Francisco area, southward in hills of Coast Range
Artemisia californica—Coastal Sagebrush													2	2	2	Occasional in few scattered localities

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<i>Artemisia dracunculoides</i> —Dragon Sagewort					2		Local in few areas
<i>Artemisia tridentata</i> ssp. <i>Field Sage</i>			✓	✓	3		Native; along coastal sand dunes
<i>Artemisia tridentata</i> ssp. <i>Musgravei</i>		✓	✓	✓	3		Native; common and widely distributed in California
<i>Artemisia tridentata</i> and vars.—Common Sagebrush		✓	✓	✓	3		Native; chiefly a Great Basin shrub but in northern California on eastern slope of Sierra Nevada
<i>Helianthus</i> (Sunflower Tribe)							Many acres cultivated and weeds widely distributed in semi-moist areas
<i>Helianthus</i> spp.—Sunflower			✓	✓	1		
Asteraceae							
<i>Solidago</i> spp.—Golden Rod			✓	✓	1		Native; 6 to 8 species, marshes, streamlands, sandy hills throughout the area
Euphorbiaceae							
<i>Ricinus communis</i> —Castorbean		✓	✓	✓	1		Introduced; cultivated as an ornamental and often escaped
Cultivated Flowers							
<i>Asters</i> , <i>Chrysanthemum</i> , <i>Cosmos</i> , <i>Daisies</i> , <i>Dahlia</i> , <i>Sunflower</i> , etc.	✓	✓	✓	✓	1		
Roses	✓	✓	✓	✓	1		

BOTANICAL SURVEY—ROWE

The following considerations and information about the various pollens listed in this article are of interest:

1. The size of skin reactions does not determine the degree of clinical sensitivity. Large reactions may occur without any clinical allergy due to past or potential clinical allergy or to non-specific causes. Small or negative reactions may occur to pollens producing moderate or severe manifestations. This is particularly true, in the writer's experience, in atopic dermatitis. Therefore knowledge of all of the pollens of marked, moderate or even slight importance in a patient's area is necessary.

2. The frequency of pollen-producing plants in the patient's living or working areas must be known by the allergist or physician treating the patient. This may require a personal local survey, especially of the trees, which vary so greatly in different areas. Common trees, such as oak, sycamore, elm, and acacia or uncommon trees, such as ash, pecan, chestnut, castor bean or mulberry, may be productive of allergy in different areas. Cultivated flowers and flowering shrubs especially privet and cotoneaster, are abundant in Northern California and may cause allergy if the patient is in close contact with them or lives near them. This writer has found that flower pollens are of special importance because of their abundance in the gardens around most of the homes in Northern California or in those areas where flowers are raised in great abundance for seeds. Grasses grown for lawns in parks or golf courses or as crops for food or seeds also need consideration. Clinical results and laboratory experiments, moreover, indicate that pollinosis to grasses may be specific for species rather than for tribes. It is most important to remember that pollen will blow for miles and that it will be suspended in the air for days or weeks. Failure to protect the patient with environmental control or with desensitization to all the allergenic pollens in the patient's environments may be responsible for poor results.

3. It is most important to study the pollens of greatest and moderate frequency listed in a patient's living and working areas and pollinating during the seasons of the patient's symptoms. Pollens of lesser importance will need consideration according to the physician's or patient's regional survey. The clinical importance of pollens in any area must finally be determined by their clinical effect and results of desensitization.

A discussion of the three great local areas of Northern California follows:

COASTAL AREA

In contrast to the southern portion of the coastal area, the northern part has an increasing amount of fir, pine, Oregon ash, redwood, alder and tanoak trees, and timothy, orchard, velvet, agrostis and sweet vernal grasses. Valley oak is less common than in the Central Valley; in the foothills interior live oak occurs. Occasional pine pollen allergy⁸ requires study of pine and other conifers. Recently a large reaction was obtained to fir pollen, which caused definite bronchial asthma in one of the writer's patients. Coastal sagebrush is only found in the coastal area, and mugwort is very common. In the sand dunes from San Luis Obispo to Eureka grows *Artemisia pycnocephala*. *Franseria chamissonis* and *bipinnatifida* also grow in the sand dunes. In the salt marshes and alkaline soils *Atriplex*

BOTANICAL SURVEY—ROWE

patula is abundant, while *Atriplex argenta* and *lentiformis* are infrequent. Covering the salt marshes is *Salicornia ambigua*. Proven cases of *Scirpus* allergy are lacking, accounting for the omission of *Scirpus* species in these tables. The writer has one patient with asthma who gives a positive reaction to *Scirpus* and whose history suggests allergy to this pollen. Clinical allergy may arise from the pollens of fruit trees, wheat, oat and mustard fields, cultivated sugar beets and other cultivated vegetations. Walnut and olive groves, of course, which are common in the coastal area, cause serious clinical allergy.

CENTRAL VALLEY AND FOOTHILL AREAS

The chart lists the many varieties of trees in this area. In the Valley itself sycamores, native oaks and walnuts are common. In the canyons and slopes of the lateral mountains alders and conifers occur. In the upper areas great conifer forests are prevalent. In the cities and towns elm, sycamore, black walnut and other less common listed trees are planted for shade and decoration. As already discussed, the physician must make a local survey of the environment of the patient to determine the actual trees that need consideration in varying degrees. In the Valley walnut, olive and fruit trees are abundantly cultivated and require local, individual consideration.

Bermuda and ray grasses are of greatest importance; Kentucky blue, oat, brome and wild rye grasses are of moderate importance. In local areas salt grasses and Johnson grass need study. Orchard, velvet, phleum and agrostis grasses are found in parks and lawns and are cultivated in pastures in the high mountains. Wheat, oats, corn, alfalfa, clover and barley are largely cultivated. Allergy to alfalfa may be severe. Though rice is widely grown in the Sacramento Valley, it seems of no clinical importance since it is self-pollinated. Because of the increasing cultivation in the San Joaquin Valley where rainfall is slight and because of the cultivation of the islands in the delta areas of the rivers in mid-California, dust and peat storms are common and cause severe discomfort and aggravate nasal and bronchial allergy. The presence of the spores of fungi in these dusts, particularly in the peat dust, requires special study. In the Central Valley the important weeds are listed in the chart. The less frequent species of *Amaranthus*, *Atriplex* and *Chenopodium* pollens may require individual consideration. In the San Joaquin Valley *Atriplex polycarpa* only occurs. Western ragweed is abundant in many areas throughout the Central Valley, and the only false ragweed is *Franseria acanthricarpa*. Coastal sagebrush is absent, mugwort being the only important *Artemesia*. A regional challenge exists in those weeds growing in alkaline areas.

EASTERN CASCADE AND SIERRA AREAS

Birch, willow, locust, elm, cottonwood, and in the north, ash trees vary

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in different areas. Box elder, aspen and conifers at times cause allergy. The physician must determine the frequency of the grasses of marked and moderate importance in each area. Only the response to therapy will indicate the degree of clinical allergy to such grasses.

Russian thistle, Western ragweed, mountain sage and greasewood, together with other listed weeds gradually increase in the desert areas near Nevada. The occurrence of weeds depends upon elevation and moisture. There is an absence of sagebrush in the dry areas. Thus, the local flora must be studied by the physician, though pollens may blow, of course, for long distances.

MOLDS

In Northern California mold allergy is of minor importance to pollen allergy. In the coastal area *Hormodendrum* is most frequent, and *Alternaria*, *Penicillium*, *Aspergillus* and *Sporotrichum* are less common fungi which occur in varying degrees. *Alternaria* and smuts increase, of course, where grains are cultivated. In damp living and working environments, especially in the north coastal areas, mold allergy needs special consideration. In the Stockton area, where storms of peat dust which contain spores of fungi are common, attempts to demonstrate allergy to such spores have met with little success.

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The ANNALS is not just another journal, but the official organ of a liberal College. One of its functions, besides the educational material it contains, is to keep its members informed of the important events which are transpiring from time to time in the College. If you would do this, much correspondence would be eliminated answering questions which have been previously published in the ANNALS.

Mark on your desk calendar the dates of the convention. It is not an uncommon experience to receive inquiries as to when and where the convention is going to be held, when previous issues of the ANNALS have contained numerous notices.

PROBABLE ROLE OF AIRBORNE SOIL BACTERIA IN PERENNIAL HAY FEVER AND ASTHMA

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THE purpose of this presentation is to report the considerations upon which is based my concept that airborne soil bacteria are probably a significant factor in perennial hay fever and asthma. I shall apologize at the onset for the failure of this paper to conform to the statistical evaluation of any clinical or research problem, but I shall attempt to present the reasons for some of this as I progress from point to point.

I should like to mention that the fundamental idea behind this thought was given to me by an abstract read in an unidentified journal seven or eight years ago. The title of this paper, the name of the author, the reference to the journal in which the original appeared, and the reference to the journal in which the abstract appeared have been lost from my files. The correct reference to this original paper will, undoubtedly, be called to my attention by someone familiar with it when this paper is published. There is also the paper of Schonwald and Deppe¹ detailing their experiences with airborne bacteria as allergens, which somewhat parallels my own experience.

The reason for my interest in this problem stems from the fact that in the semi-arid Southwest, comprising West Texas, New Mexico, Arizona, and parts of Southern California, one of the worst features of the climate is the occurrence of periodic, rather violent dust storms, with wind velocities ranging between thirty-five and forty-five miles per hour, and sometimes with velocities going considerably higher. These winds blow large clouds of the surface soil into the air, and altogether these storms present quite a nuisance for the inhabitants of this area.

In observing hay fever and asthma patients it became apparent to me, after a short time in this locality, that these patients divided themselves sharply into two major groups with reference to the dust storms: namely, those who apparently had no more difficulty on those days than on other days (their inconvenience was of the order of the inconvenience experienced by the population at large), and those who complained bitterly of exacerbations of hay fever and/or asthma incident to these storms; this seemed to occur quite irrespective of the season of the year at which the dust cloud occurred.

A number of years were spent trying to correlate these cases with some factor incident to these storms. It was thought for a time that the fungus content of this dust was perhaps a factor. However, it was not possible to correlate the fungi found with the skin sensitivity of these patients.

Approved for publication June 30, 1952.

AIRBORNE SOIL BACTERIA—DUTTON

Numerous microscopic examinations of collected dusts were made in an effort to find some organic particle which could be identified. This search was fruitless. Also, following a technique which had been helpful in some cases of fungus spore sensitivity, washings from the nasal passage after exposure to the dust were searched carefully for accumulations of fungus spores or other known antigenic material. This proved to be entirely unsuccessful. An attempt was made to correlate this with variation in barometric pressure. Their being a rather sharp drop just preceding the storm. This, however, did not seem quite tenable. As a general rule, the barometric pressure drops sharply from six to eight hours preceding the development of the wind. No exacerbation of symptoms was experienced during this period, although an occasional individual did present the appearance of being aware of barometric pressure, by being able to foretell dust storms without benefit of barometric pressure readings. A number of inhabitants of this general area have a very definite emotional response to these dust storms. This is an indefinable type of psychological reaction, but an attempt was made to correlate this psychosomatic, probability without success.

Much of my own concept concerning the probability of bacterial antigen being responsible for some of these unexplained symptoms has grown gradually through the years from repeated study of puzzling, unexplained clinical patterns, detailed observations on a few selected cases, and fragmentary observations on many patients. It is, therefore, difficult to reduce this data to tabular form, and I shall make no effort to do so.

The method of the planned study was to make plate exposures with an arbitrary interval of fifteen minutes, using a medium suitable for non-pathogenic organisms, the technique being much the same as that for the familiar plate exposures for fungus studies. On an average day, the bacterial count, after twenty-four hours' incubation on these plates, ranged between twenty-five and fifty. On dust storm days, a similar exposure raised the bacterial count on these plates from 3,000 to 5,000. Various types of suspensions of these organisms were made, as in the preparation of the usual vaccine. Some of these were made by isolating the predominant bacterial types and growing them in pure cultures, while other suspensions were made by washing the plate of the entire growth. These were done before any concomitant strains of fungi had opportunity to grow. These suspensions were diluted to an opacity corresponding with the usual bacterial vaccine. A few were suspended in concentrations several times the usual strength of bacterial vaccine.

The skin testing was done by the intradermal method, using a 1:100 dilution of this concentrated suspension. If this resulted in a negative reaction, the 1:10 dilution was utilized and then the full strength, successively. A number of patients were found who gave definite immediate wheal positive reactions to as little as 1:100,000 dilution of this concentrated vaccine.

AIRBORNE SOIL BACTERIA—DUTTON

The tests were all read at twenty minutes and were recorded in the usual manner as 1, 2, 3, and 4 plus. No true tuberculin delayed-type reactions were observed. A few irritative reactions persisted over a period of twenty-four to forty-eight hours, but they lacked the characteristics of the tuberculin-type reaction. A total of about 400 patients have been tested with these suspensions. There has been quite definite readability, there being little in the way of irritative phenomena, and the negative reactions have been quite clear cut.

In each of these cases an effort has been made to establish the clinical reaction to dust as it occurs in these dust storms. In those individuals who apparently had no flare-up of clinical symptoms during the dust storm period, positive reactions were apparent in about 5 per cent of the cases. Of those individuals who did have clinical flare-ups of nasal or bronchial symptoms incident to dust storms, about 80 per cent responded with positive skin reactions. In a few instances, individuals, who were clinically sensitive to house dust, but skin negative to house dust testing and unresponsive to house dust treatment, were given vaccines made of a similar nature by shaking house dust samples over the plate. These patients reacted with positive skin reactions.

In these patients who gave a clinical history of dust storm flare-ups and who gave positive skin reactions to these suspensions, treatment was instituted, starting usually with a 1:10,000 dilution of this suspension and gradually increasing, as is usual with pollen therapy. A number of apparent pollen cases, that had been under treatment with pollens but failed to respond with satisfactory clinical improvement, appeared to make quite satisfactory improvement after instituting the vaccine therapy.

A total of seventy-five cases were found to be suitable for treatment. Roughly, half of these patients made apparent clinical improvement under treatment. A number of them were not followed, due to various circumstances, for a sufficient period of time to gauge therapeutic effects. None of the patients who did respond apparently satisfactorily were treated with these suspensions alone. They had received pollen therapy and other indicated therapy, as usual. It is, therefore, impossible to reduce one's impression of therapeutic effectiveness to statistical values, and it is obvious that estimation of improvement due to the use of these vaccines is based on general impression only. A few individuals were deliberately, but cautiously, over-dosed, and in several, flare-ups of symptoms occurred.

We are quite aware of the crude nature of these bacterial suspensions and their lack of reproducibility from one batch to the next. It is, therefore, thought that only minimal therapeutic help may well be of significance.

The philosophical aspects of this question bring up several other points. The clinical behavior patterns of certain patients, that all of us see, have been without solution; for instance, the problem of the sharply defined geographical limits within which symptoms occur in certain patients, but

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do not seem to correlate with botanical distribution or other recognizable allergenic exposures. The clinically house dust sensitive cases, without positive skin test to house dust and with negative response to house dust treatment, have baffled us. Three individuals who were amateur gardeners had rather marked symptoms on exposure to soil, but with no demonstrable sensitivity to the plants worked with.

Another philosophical consideration, in my own mind, concerning this, is the failure to conceive of a valid theoretical objection to the concept of allergy to these bacteria. From this work we have, therefore, emerged with the conviction that airborne soil bacteria probably are capable of acting as allergens, that some individuals actually exhibit symptoms of allergy correlated with varying exposures to these bacteria, and that therapy along this approach is sometimes helpful. One realizes, of course, that this is little more than a theoretical concept.

There are multiple problems to be solved before these observations will realize validity. These are similar to those that have arisen in the field of fungus allergy; namely, a systematic analysis of the bacterial content of the air, seasonal variations, and geographical variations.

There are, likewise, many technical problems involved. The preparation of adequate testing and treatment materials is vital but is not nearly so simple as the preparation of pollen extracts, for instance. There need to be chemical studies of bacterial compositions. There need to be demonstrations of the antigenic capacity of these bacteria by experimental means. There need to be adequate classification studies. There needs to be a means devised to calculate the number of nonviable cells of these organisms and cells of those strains that fail to grow on the usual media. There needs to be experimental studies to select suitable media, exposure times, incubation times, and temperatures for eliciting the best growth. Experimental determination of antigenic specificity or cross reactions between closely related organisms in this group need to be made. Adequately controlled skin testing of a large group of patients needs to be done. Adequately controlled efforts at treatment of a large number of patients will be necessary. Individuals who apparently have a sensitivity only to these bacteria, so that experimental observations of therapeutic results would be more conclusive, need to be sought out.

In this general community it has been observed frequently, in casual conversation with many people, that they have hay fever only when the sand storms blow. Obviously, these people do not seek medical help, but accept their burden as incident to the distressing amount of sand in the air. Some of these might be enlisted as volunteer subjects. It is evident that these problems can be adequately and rapidly evaluated only by cooperative research.

I hope I may be pardoned for omitting long tables of "facts and figures" for statistical evaluation. This has been by intent, for it seems that such

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would lend apparent exactness to a group of very inexact observations. This inexactness has been due to the very gradually developing awareness of the probability of my conclusions; the utilization for several years of highly selected cases for study; the inability to certify that successive batches of testing material were similar antigenically as to specificity and capacity; the utilization of a group of patients whom, for obvious reasons, it has not been possible, in all cases, to follow for a sufficient length of time; and the inability to exclude the factors of diet, dust, pollen desensitization, or other therapeutic efforts. Also, there has been a variation from year to year and season to season in the completeness of my efforts, due to various factors concerned with the pressure of private practice. I feel sure that a statistical breakdown of my data would be inexact and probably misleading.

Nevertheless, I do have the rather firm personal conviction that there is sufficient evidence to warrant the belief that the airborne soil bacteria are a factor in certain allergic problems and that my tentative conclusions possess a measure of validity, as yet to be quantitated.

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THE SHAPE OF THINGS TO COME

Recent literature shows that a number of new medicines, as yet unlisted, are being prepared for distribution in the treatment of bronchial asthma.

Tyral tablets, which contain l-tyrosine (200 mg), Pyridoxine hydrochloride (2.5 mg) and Niacinamide (10 mg) will soon be offered for the treatment of allergic disorders.

Being evaluated clinically at this time are Cardalin tablets, each of which contains aminophyllin (5 gr), aluminum hydroxide ($2\frac{1}{2}$ gr.) and benzocaine ($\frac{1}{4}$ gr) for the treatment of bronchial asthma by the oral ingestion of doses of aminophyllin sufficiently large to be absorbed and cause therapeutic effects, but without the usual nausea.

German research scientists have combined Khellin and Theophylline, in proportions of 20 mg of the first, and 100 mg of the second, in a liquid available in 10 cc ampoules, for the treatment of bronchial asthma by injection. In this country, Khellin has been used with indifferent success and inconstant results. It will be interesting to see what happens when Khellin and Theophyllin are injected together.

PROPHYLACTIC TREATMENT OF SOME TYPES OF HEADACHE

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CHRONIC headache mirrors a physiologic change or alteration occurring with numerous syndromes. Despite more recent classifications and attempts at clearly demonstrated definitions of these symptom-complexes, considerable misunderstanding and controversy still exist as to the mechanism and origin of headaches. Naturally, the list of remedies is long and confusing. Some drugs may be used for their pain-lessening ability, or others may be used in an attempt to restore a pathophysiological process to normal.

The patient's immediate concern is relief, so the physician, after considering the cause of the headache, commences procedures of elimination and alleviation. Migraine and its equivalents and variants, together with tension headache in particular, are by far the most frequently encountered headaches. Attempts to separate these as restricted entities offer difficulties when prescribing medication.

Ogden⁵ has shown statistically that persons with headache have a higher incidence of various respiratory symptoms, and that there is also a significantly higher familial history of allergy in these individuals. These background factors frequently go along with emotional or occupational problems.

Whether all or some migraine headaches are allergic in nature assumes less significance when treating with drugs, since most headaches are considered to be vascular in type and are the result of dilatation of the extracranial or intracranial arteries, together with an increased amplitude of pulsation of the vessels. The autonomic nervous system basically controls the action of these vessels. (In this connection, it is interesting that the hormones ACTH and cortisone are now considered to have their ultimate effect upon the sympathetic nervous system.) Ergotamine tartrate, dihydroergotamine (D.H.E. 45) and Cafergot (a combination of ergotamine tartrate with caffeine) have been found the drugs of choice when treating vascular headache.^{1,3,4,6}

The writer first used Bellergal* in 1948 for preventive treatment of headache (see Case 1). Bellergal is a combination of ergotamine tartrate, a sympathetic inhibitor; Bellafoline, a parasympathetic inhibitor; and phenobarbital, a central and subcortical sedative. Through the action of the three components of Bellergal, an inhibitory action is exerted on all three divisions of the neurovegetative system, thus relieving those somatic disorders which are related to autonomic dysfunction.

Tension itself may initiate the headaches, or act as a "trigger" mechanism.

*Sandoz Pharmaceuticals.

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Patients with tension headaches benefit by interval treatment with psychotherapy and medication directed toward regulation of the autonomic nervous system.

Hilsinger,² in 1951, reported the results of the use of Bellergal in the interval treatment of twenty-five patients suffering from migraine, tension headaches, or histaminic cephalgia, with 68 per cent excellent results, 12 per cent good results and 20 per cent poor results, and found the drug to prolong the quiescent period between the acute attacks of vascular headache.

The results of the use of Bellergal in the prophylactic treatment of some types of headache are herewith presented. A number of these patients had previously received ergotamine, dihydroergotamine, or Cafergot as immediate therapy. The cases were carefully screened as to type of headache—migraine, migraine equivalents and variants, histaminic cephalgia and tension headaches. The average age was early in the fourth decade of life. There were nearly twice as many females as males. The group represents mostly allergic patients who had low tolerance to the more commonly used vasoconstrictors, and in whom an attempt to reduce incidence and severity of headache was considered essential.

DOSAGE

The dosage of Bellergal was based upon the clinical response of the patient to treatment initiated at the acute stage and continued with a view to prophylaxis. Dosage consisted of one tablet every three hours, preferably before meals, to a maximum of six tablets daily. This was then reduced to one tablet fifteen minutes before each meal and at bedtime, and then to the smallest effective dose which was established by experimentation in each case. This maintenance dose was continued for three out of each four weeks and was considered the interval treatment.

CASE REPORTS

Case 1.—M. H., housewife, age 54. First seen September, 1948. Mother had severe recurrent "sick headaches" and one sister suffered severe headaches. Familial history of hay fever. Has had headaches for many years and during the past two years, following menopause, headaches have become more frequent. Average incidence, three weeks. Headache usually occurs on either side (temporal). Awakens with severe pain which becomes much worse on moving about. No flushing or sweating on affected side. No tinnitus or aura. Becomes apprehensive of impending attacks and frequently gets them when nervous or fatigued. Married second time; second marriage disappointing. Has always been active. Interested in music. First husband very sympathetic. Now has a fear complex. Basal metabolism, blood pressure, blood and urinary findings normal. Because of the strong familial history of allergy, a large series of intradermal tests were done with foods and miscellaneous inhalants. There was a mild response to house dust and several of its components. Food tests were negative, except chocolate. An individual food test with chocolate induced an attack of headache. Gynergen gave unsatisfactory results. One tablet of Bellergal every four hours for six doses gave good, but not complete, relief. Premarin® 0.625 mg daily along with Bellergal three tablets daily gave complete

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relief from the headaches. A three-weeks' regime of this therapy with gradual reduction of the dosage to one tablet daily has prevented recurrence of all attacks since then.

Apparently this case is a syndrome, frequently encountered by the allergist, in which allergic, endocrine and tension components are all contributing factors. It is difficult to make a sharp demarcation in classifying. This case is presented as one in which Bellergal, used with an estrogenic substance, can be expected to give excellent results.

Case 4.—M. M., female, single, age 30. Perennial allergic rhinitis, occasional wheezing, recurrent hives and severe unilateral headaches of twelve years' duration. Brother gets migraine headaches. Patient develops nasal blocking and thin nasal discharge at onset of headaches. Headaches were becoming progressively worse and recently occurred almost daily for two or three weeks at a time. Patient holds a responsible position and emotional episodes will at times induce headaches. After exploring sinuses and examining the eyes, a nose and throat specialist diagnosed her symptoms as being caused by an allergy. The smell of certain perfumes may precipitate an attack. Patient discovered that banana or chocolate will definitely induce a headache. The legume family, strawberries, and members of the cabbage family all aggravate the nasal symptoms. Intradermal tests with common inhalant offenders were negative. Patient's general condition was good. Elimination of offending foods greatly improved nasal symptoms. An antihistamine helped the nasal symptoms but not the headaches. Empirin Compound with codeine lowered the threshold to pain. Cafergot also relieved, but "nearly knocked her out." Bellergal was begun with one tablet every four hours for four doses during the day following her last headache, and gradually reduced to three tablets daily for three weeks of each month. There have been no headaches for three months, which is the longest interval in twelve years. Patient's nasal symptoms have also disappeared except during a severe middle ear infection associated with a purulent nasal discharge. Both cleared promptly with Terramycin.

Case 7.—C. J. male, age 46. Frequent recurrent headaches which awakened him from a sound sleep towards morning. Headaches extremely severe, unilateral along temporal region associated with sweating and flushing of the skin on that side of the face, lacrimation and congestion of the eyes, and nasal stuffiness. The excruciating pains also involved the neck. These episodes occurred almost daily. The headache could be histamine-induced. Cafergot gave considerable relief but made the patient dizzy. Bellergal was prescribed fifteen minutes before meals and at bedtime, then gradually reduced to three and later to two tablets daily. Patient has had no recurrence of histamine cephalgia for twelve weeks.

Case 11.—J. K., female, age 38, farmer's wife. For the past seven years has had perennial allergic rhinitis, bronchial asthma worse in the winter or when exposed to barn dust, and severe recurrent frontal headaches associated with weakness and nausea. Intradermal skin tests showed marked reactions to environmental (farm, house and barn) dusts, and common air molds. Individual food tests revealed nasal allergy accompanied by wheezing and/or frontal headache and nausea. The single ingestion of milk, rye bread, corn products, celery, peanuts, peaches and strawberries would produce one or more of the above-mentioned symptoms. Except for a moderate eosinophilia, and typical allergic-appearing nasal mucous membranes, the physical examination including routine blood counts, urinalysis and x-rays, was negative. She states she has been very nervous for many years. For a hard-working farm woman who worked in the fields, an elimination diet was difficult to follow, and a good appetite resulted in indiscretions of food intake. Immunization injections consisting of the offending inhalants and an antihistamine greatly relieved the respiratory

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symptoms. Her headaches were also relieved by Cafergot but she seemed to be more nervous following a course of this combination. Ten weeks prior to this report, Bellergal was commenced as interval therapy in the usual doses. The headaches, formerly occurring on an average of two to three weekly, have not recurred except once when she disregarded her diet.

Case 14.—B. D., female, age 32, department store buyer. Had severe migraine-like unilateral headaches since twenty-five years old, now becoming more severe, accompanied by nausea, a fainting feeling and preceded by blurring of vision. Has had symptoms of nasal allergy, worse in the winter. There was a strong positive maternal history of headaches for many years, and one aunt had migraine. Patient definitely associated headaches after the ingestion of wheat, peanut, chocolate, pork, lettuce, spinach, and occasionally milk. Intradermal tests showed positive reactions to chocolate, banana, grape, onion, spinach, pork and peanut. An elimination diet was prescribed and on rare occasions when her occupation would allow her to remain home, strict diet restrictions resulted in complete freedom from headaches. Since she was being entertained on her frequent trips, it was impossible for her to avoid foods which caused the headaches. Bellergal was prescribed as interval treatment with remarkably favorable results. She has had no migraine for fourteen months although has had an occasional headache when under unusual tension, or fatigued from loss of sleep.

Case 18.—M. W., housewife, age 42. No history of allergy in the immediate family. Her mother at one time suffered a nervous breakdown. When exposed to bright sunlight patient sneezes and her nose blocks. Patient has been very nervous and apprehensive the past five years since her husband has become addicted to alcohol. When the latter is not drinking he is good-natured and patient becomes free of headaches. When the husband is on a "spree," he becomes quarrelsome, belligerent, and on occasions has physically abused her. During the past year the patient has become in constant fear of him and when he returns home intoxicated she frequently develops sharp, steady headaches, variable in location—frontal, occipital or bilateral. No aura or nausea. The severe pains would last for several hours unless relieved by an analgesic such as Empirin Compound containing a grain of codeine. Various antihistamines were tried, as well as ergotamine and other drugs used to relieve vascular headaches. A tablet of Bellergal four to six times daily failed to prevent recurrences or severity of attacks. All intradermal tests with common food offenders were negative or doubtful. Apparently this patient's headaches are due primarily to psychological factors and her relief lies not with drug therapy but in curing her husband.

RESULTS

Six cases are reported illustrating the types of headaches encountered in a series of headache cases, mostly of allergic origin and vascular in type, which were treated with Bellergal. It is difficult to clearly classify many of these headaches with varying syndromes, but a rather close scrutiny of the histories of the thirty-five case studies would justify placing them in the following categories:

Type of Headache	No. of Patients	Results		
		Good	Fair	Not Relieved
Tension (primarily).....	2	2		
Allergic (including mixed types)....	30	25	3	2
Histaminic	2	1	1	
Psychogenic	1			1

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DISCUSSION AND CONCLUSIONS

Although the incidence of tension headaches or headaches of emotional origin *per se* are relatively more frequent than other types of vascular headaches, they were comparatively infrequent as observed in a clinic where practically all of the patients were seeking relief from allergies of all kinds in which headache was a concomitant symptom. Those few seeking relief from headache alone did so thinking that the headache was due to an allergy because there was a history of allergy in the family, or they also had minor allergic symptoms.

Many allergic patients have an intelligence quotient above the average and have a tendency to be nervous or even psychoneurotic. This group of patients with multiple allergies who sought relief from their headaches averaged more emotional trends and sensitivity to stimuli, had a lowered threshold to endurance of emotional strain, and were of the worrisome type. They required more than environmental control and immunization measures to obtain relief not only from the acute attack but to shorten the duration of, and lengthen their freedom from, their distressing and often disabling symptoms. Sedation alone would not control the headache attacks of these patients who were receiving orthodox allergy therapy. The anti-histamines were disappointing and frequently contraindicated.

A rationale was thus established whereby better therapeutic results could be expected from a logical combination of drugs in order to secure total inhibition of autonomic overactivity, which was considered a cardinal feature of these cases. Bellergal met this requirement in the small group of allergic patients herein reported better than any other drug therapy used, and there were no appreciable side effects during the four years of its use in treating headaches.

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A CLINICAL REPORT ON THE USE OF DIBISTINE IN THE TREATMENT OF ALLERGIES

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THE combined use of drugs for their enhanced therapeutic value is a very old practice. Since the discovery of the antibiotics and the antihistamines there has been a renewed interest in the subject. Positive summation or synergism is frequently used to reduce the untoward side effects of similarly acting drugs with a common factor. Thus, when treating an infection with sulfathiazole in three gram doses, the kidney tubules may become blocked with the excreted drug. A combination of sulfathiazole, sulfamerazine and sulfadiazene in combined doses of one gram each has the same antibacterial effect without any precipitation in the kidneys.⁴

Also, the supplementary combination of a slowly acting drug with a rapidly acting one of similar nature may increase their effectiveness. On the other hand, Winter⁷ found that the antihistamines have a potentiating effect on the sedative action of barbiturates, and the coincident ingestion of barbiturates and antihistamines must be used with caution. Similarly, such a combination with an excitant such as ephedrine and its congeners if not properly balanced, or because of individual susceptibility, becomes antagonistic and may be responsible for the intolerance of such combinations in certain patients.

Hubbard and Berger³ combined two antihistamines made by different manufacturers in the treatment of vasomotor rhinitis in order to balance the stimulating effect of the one against the sedative effect of the other. They found the combination of these two drugs gave better relief than when they were used separately. When combining the drugs side reactions occurred equal to those of the stimulating antihistamine but exceeded that of the antihistamine with a sedative effect. Their combined use gave as many severe side reactions as with the sedative antihistamine, but considerably less untoward reactions than noted with the stimulating antihistamine. Hubbard and Berger explained these results as being due to an antagonism, however incomplete, in the unfavorable reactions of the two antihistamines.

Both Antistine or antazoline hydrochloride and Pyribenzamine or tripelennamine are derivatives of ethylenediamine. The common factor of antihistamines is essentially the ethylamine structure. However, Antistine is in the form of a ring compound instead of a "straight chain." The ethylamine base corresponds to the side chain of the histamine molecule and to part of the imidazole chain.

It is logical to expect that the combination of two antihistamines such as Pyribenzamine and Antistine, the latter, when used separately, repeatedly causing less side reactions than the former, would show advantageous

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clinical results.^{1,5} Arbesman noted that by decreasing to a smaller level the dosage of Pyribenzamine which remained effective, side reactions could be avoided. Therefore, the regular prescribed dose of Pyribenzamine, when used alone, of 50 mg and that of Antistine, 100 mg, were both halved and combined in one tablet containing 25 mg tripeleannamine and 50 mg of antazoline hydrochloride and called Dibistine.®* This combination would be expected to cover a wider spectrum of allergic diseases since each drug separately has been shown to be better than the other when treating certain allergic syndromes. A clinical study was, therefore, taken of the effects of Dibistine when treating a variety of allergic symptoms. These effects have been compared with previous experiences with a variety of other antihistamines when treating the same conditions since the introduction of the first antihistamine, Antergan, by Halpern.²

Simon and Toohey⁶ recently reported their clinical experiences with Dibistine in allergic states. Of their series of fifty cases 92 per cent were improved while 6 per cent showed undesirable side effects which were mild, consisting of drowsiness and depression.

The use of Dibistine was commenced March 6, 1952. Most of these patients had previously taken antihistamines of one or more kinds so that a collateral group was treated as usual, with the antihistamine with which they obtained the most relief from their specific allergies. One group, patients who were previously doing well on Chlor-Trimeton Maleate® were changed over to Dibistine, and another small group received Chlor-Trimeton Maleate alone. The patients previously treated successfully with Chlor-Trimeton Maleate with no side reactions, were given one tablet of Dibistine three times a day and all of their allergic symptoms were controlled as satisfactorily as when using Chlor-Trimeton Maleate.

When comparing the therapeutic results of Dibistine with those of other antihistamines, an effort was made to select patients with fairly equal clinical symptoms. Efforts were made to select patients with symptoms of equal severity when comparing the effect of one antihistamine with that of another. Minnesota had a comparatively severe tree-pollinating season starting about April 1, which provided opportunity to give fifteen tree pollen sensitive patients who had previously been treated by immunization measures, a good trial with the use of Dibistine. All fifteen cases showed marked relief from the hayfever, and no other treatment such as the use of nasal instillations or ephedrine was necessary. Only one case in this group complained of drowsiness.

The grass pollens start causing symptoms in Minnesota about the first of June and last until the middle of July. Although the pollen counts of grass and ragweed were comparatively low, as a result of frequent rainfalls, respiratory symptoms were severe. This was either due to a relatively toxic pollen and/or an extremely high incidence of the common atmospheric

*Product of Ciba Pharmaceutical Products, Inc., Summit, N. J.

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mold offenders like *Alternaria* and *Hormodendrum*, particularly during July.

Twenty-two grass sensitive patients, the majority of whom were also sensitive to ragweed, were treated throughout the season with Dibistine. The majority of these patients had been treated one or two seasons previously by immunization measures and had also received other antihistamines. This group presented mild to moderate symptoms depending upon the length of time of previous preseasonal use of antigen protection measures. Coseasonal immunization measures were not used in this group. Twenty of the series showed good results using coseasonal treatment with Dibistine alone, and two moderate improvement. Two patients complained of some drowsiness or depression but not sufficient to discontinue treatment.

Ragweed sensitive patients began to have symptoms the first week in August, and at this writing the pollen count is only thirteen to the square centimeter. Regardless of previous immunization and avoidance measures only those who presented respiratory symptoms during this time were treated with Dibistine. Some patients also had asthma during the season. Thirty of the Fall type of seasonal allergic rhinitis patients received Dibistine alone as symptomatic treatment. Others, for comparison, were treated with various previously used antihistamines. Because of extreme weather changes in Minnesota about 75 per cent of the patients with pollen allergic rhinitis have perennial allergic respiratory symptoms, either allergic rhinitis and/or bronchial asthma. About one-fourth of this group also have mixed or infective asthma.

It is necessary to treat these latter complicated Fall type of cases with concomitant allergic measures. Ephedrine or its congeners was used in one form or another for some, as well as antibiotics when the infective element was present. This report does not include the latter type.

In the cases of perennial allergic rhinitis who also had bronchial asthma, potassium iodide, or other expectorant tolerated, was prescribed in order to prevent any drying effect on the bronchial secretions.

Of the thirty patients with seasonal allergic rhinitis who were treated with Dibistine alone, twenty-six showed good results, one fair results, and three no appreciable improvement. Two patients complained of mild drowsiness or dryness in the nose.

In nine cases of atopic dermatitis the pruritus was sufficiently controlled to avoid scratching and gave the patient adequate relief. At night for sedation they were given Benadryl or Pyribenzamine in full doses.

Three cases of urticaria and one of angioedema showed satisfactory improvement with Dibistine.

Intradermal testing was done, and after the skin reactions were recorded, Dibistine was given, particularly to those who showed fairly marked local reactions, and the patients were kept in the office from one-half to one hour. At no time was it necessary to give ephedrine or epinephrine. Also

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Dibistine was dispensed to patients who were approaching the higher doses of grass and ragweed pollen extract. It was found that we could increase the dosage more rapidly without untoward reactions and give more adequate protection before the season. All of these patients were observed in private practice and the results tabulated from time to time on successive visits.

It was of interest to note that comparatively young children can tolerate the regular dosage of Dibistine very well without side reactions. This series of twelve patients is, of course, too small for comparison with other antihistamines used, but the impression was obtained that Dibistine was tolerated just as well, if not slightly better, by children.

SUMMARY AND CONCLUSIONS

Dibistine proved in this small series to be as effective as other various antihistamines used, without, as a rule, as many unfavorable reactions. The average dose was three tablets daily. The combination of two antihistamines, the regular dose of each halved, proved more effective with less side reactions than when each was used singly in the full regular dose. There seems to be a better balanced summation effect with Dibistine than that effected by the use of a single antihistamine or previous combinations of antihistamines.

Following these trends may lead to other avenues of investigation of direct antihistaminic activity.

The fact remains at present that protection by elimination, immunization and adjustment measures is the primary therapy, but when this fails the improved antihistamines afford equal, if not better, symptomatic relief than the adrenergic sympathomimetic stimulants whose side effects frequently prevent their use in adequate dosage.

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TERRAMYCIN IN INFECTIOUS ASTHMA

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THERE are many patients with bronchial asthma whose attacks are preceded or accompanied by an upper respiratory infection. Twenty such patients, taken from office practice, were placed on terramycin at the onset of an asthmatic attack to determine whether reducing the infective period would shorten the duration of their illness. In most cases, the upper respiratory infection was not sufficiently severe to warrant the use of an antibiotic, but it was thought that the possibility of reducing the number of days of asthma would justify the use of terramycin.

DOSAGE AND ADMINISTRATION OF TERRAMYCIN

The dosage of terramycin used in this study is small as compared to that recommended for severe infections. Each patient was given one dozen terramycin capsules (250 mg) and instructed to take two capsules at the onset of asthma and then one capsule three times a day for the next four days. Each dose was followed by two ounces of milk.

TYPE OF ASTHMA PATIENT

All twenty patients were symptom-free and negative to physical examination in the interval between their attacks of asthma. The duration of wheezing ranged from one year to twenty-five years. The ages of the group varied from three years to sixty years; there were ten males and ten females. The severity of the asthma differed in each patient but all had, at some time or another, required an injection of epinephrine for symptomatic relief.

As indicated by Table I, infection was not the only cause of asthma in seventeen of these twenty patients, but infection was the most frequent cause. Less frequent causes of asthma in this series were atopy (positive skin tests with clinical confirmation), emotional tension factors, weather changes, and physical exertion.

RESULTS

Of the twenty patients, thirteen were relieved of the asthma attack within forty-eight hours, a few within twenty-four hours. Most of these patients had noted that attacks previously would last four to seven days. Three patients were relieved of attacks in four days. Four patients were not helped by terramycin.

After the first twenty-four hours, the need for supportive medication (epinephrine, ephedrine, aminophylline and iodides) was usually lessened. Terramycin was not continued after four days in any of these patients.

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TERRAMYCIN IN INFECTIOUS ASTHMA—ROSEN

FACTORS PRODUCING ASTHMA ATTACKS

Case No.	Sex	Age	Infection	Atopy	Emotion	Weather	Exertion	Result	Complications
1	F	26	++	++	0	0	0	Asthma better 1 day	Moderate diarrhea
2	M	30	++	++	+	+	+	Asthma better 2 days	None
3	F	28	++	++	++	++	0	No improvement	None
4	M	3	++	0	0	0	0	Asthma better 2 days	None
5	M	8	++	+	+	+	+	Asthma better 2 days	None
6	F	50	+	0	++	+	+	No improvement	None
7	F	7	++	++	0	0	+	Slight improvement	None
								Chronic infected sinuses	
8	M	19	++	++	++	+	0	Asthma better 2 days	None
9	M	10	++	+	0	+	0	Asthma better 1 day	None
10	F	40	++	0	0	0	0	Asthma better 2 days	Mild diarrhea
11	M	9	++	+	0	0	0	Asthma better 3 days	None
12	F	26	++	+	0	+	++	No improvement	None
13	M	52	++	0	0	0	0	Asthma better 2 days	None
14	F	11	++	+	++	+	+	Asthma only slightly improved in 4 days	None
15	F	60	++	+	0	0	0	Asthma better 2 days	None
16	F	23	++	0	++	0	++	Slight improvement	Moderate diarrhea
17	M	53	++	+	+	0	++	Asthmatic bronchitis rather than true asthma—better in 2 days	None
18	F	32	++	+	++	++	0	Asthma better 1 day	None
19	M	35	++	0	+	0	0	No improvement—stopped terramycin after one day	Severe diarrhea
20	M	41	++	++	++	++	0	Slight improvement	None

There is another type of asthma patient who seems to have chronic sinus or lung infection as a cause of continuous long-term asthma. At a later date, the effect of terramycin administered daily over a period of many months on this type of case will be the subject of a separate report.

COMPLICATIONS OF TERRAMYCIN THERAPY

When terramycin was first made available it was prescribed without milk or antacids and the side effects such as diarrhea, nausea and vomiting were frequent and severe. In this series of twenty patients, complications were not severe, first, because the dosage was low, second, because the terramycin was used for only four days and each dose was followed by milk.

Diarrhea occurred in four patients. In one it was severe and accompanied by nausea and vomiting. This ceased within twenty-four hours after discontinuation of treatment, but moderate diarrhea continued for five days. Two patients had moderately severe diarrhea which cleared within twenty-four hours following cessation of antibiotic medication. These two patients, however, were able to take the terramycin for the prescribed four days. One patient had mild diarrhea for the first day but none on the next three days during which it was taken.

Five patients had mild itching of the rectum which lasted from two days to one week after medication was terminated.

COMMENT

The question of giving an antibiotic in the upper respiratory phase of an attack of infectious asthma is not unlike that of the upper respiratory phase which usually precedes attacks of rheumatic fever. Recent evidence^{2,4,5} seems to favor this approach in the prevention of cardiac damage

TERRAMYCIN IN INFECTIOUS ASTHMA—ROSEN

to the rheumatic patient. In infectious asthma, there have been favorable reports on the use of the sulfonamides³ and penicillin¹ to abort the attacks of asthma which follow infection.

CONCLUSION

Terramycin is a valuable medication in the treatment of infectious asthma. When the dosage is low and the side effects are lessened by concomitant ingestion of milk, the complications are not usually severe.

SUMMARY

Twenty patients with bronchial asthma were chosen for this study. Their attacks usually followed an upper respiratory infection, or the attack of asthma appeared concurrently with an upper respiratory infection. All were office patients treated in the routine practice of allergy. The group included five children. Their ages ranged from three years to sixty years. The duration of bronchial asthma varied from one year to twenty-five years. All the patients were symptom-free and "negative" to physical examination between attacks of asthma.

Only three of the twenty had upper respiratory infections as the sole cause of their wheezing. In addition, attacks would result in the other seventeen from atopic factors, weather changes, emotional tension, and physical exertion.

One dozen capsules of terramycin (250 mg) were given to each patient with instructions to take two capsules at the onset of wheezing and then one capsule three times a day with about one fourth of a glass of milk.

Of the twenty patients, thirteen were relieved of their attacks within forty-eight hours, a few within twenty-four hours. Most of these patients had noted that attacks previously would last four to seven days. Three patients were relieved of their attacks within four days. Four patients were not helped by terramycin.

Diarrhea occurred in four of these twenty patients in one of whom it was severe and accompanied by nausea and vomiting. In two it was of moderate severity. In the fourth patient the diarrhea was mild.

It may be concluded from this short series of patients given terramycin on only one occasion that terramycin is of value in the treatment of some patients suffering from infectious asthma.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS do not necessarily represent the group opinion of the Board or of the College.

DEFINITIONS

The meanings of words are generally drawn from their common usage, and common usage is frequently not dictated by any authority, least of all for the persons who first used the words.

Von Pirquet's term "Allergie" has come into world-wide common usage from which its *usual* meaning can be determined. First, the word implies a state of ill health. Second, the word implies a specific sensitivity; that is, the allergic state of ill health ensues upon exposure to quantities of substances which do not harm most individuals of the same species.

Unfortunately for the peace of mind of some theorists, von Pirquet was beguiled into an etymological point of view of his term and an inadequate emphasis of the fundamentally important phenomenon of specific sensitivity, which should have been, and which by common consent has become, the cornerstone of the concept of allergy. Von Pirquet's etymological definition, "altered reactivity," required the inclusion of specific immunity within the meaning of the term; which would make the word practically useless. It is very unlikely that medical scientists or science writers will see any pedagogic advantage in referring to immunity to diphtheria as an allergic condition, to say nothing of the educated laity to whom the idea of allergic *disease* is commonplace in both conversation and observation.

Attempts to define the relationship of anaphylaxis (the *experimentally* produced specific sensitivity of lower animals) to allergy have divided the theorists into three camps: those who would classify all conditions of specific sensitivity under anaphylaxis, those who consider anaphylaxis a form of allergy, and those who separate the two as forms of specific sensitivity.

The demonstration of all allergic diseases in lower animals now requires that they be distinguished from the experimental anaphylactic sensitivity.†

Some practitioners of the cutaneous tests in reaginic allergy have urged limitation of the term allergy to those specific sensitivities in which allergic antibodies have been identified as their specific mechanism. Again the powerful influence of common usage can be confidently expected to decide the fate of such a suggestion. The general medical profession and the laity will no doubt continue to refer to a specific food sensitivity as allergic in spite of the negative skin test, although there are undoubted cases in which

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†See Reddin's comprehensive summary in *Annals of the New York Academy of Sciences*, 50:692, December, 1949.

Progress in Allergy

THE ANTIGEN-ANTIBODY REACTION IN CONTACT DERMATITIS

A Hypothesis and Review

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Following the early studies of Obermayer and Pick⁷² with iodoproteins, Wolff-Eisner¹⁰¹ had presented the theory that drug allergies might be due to a sensitization with chemicals which are not antigenic by themselves, but are turned into a full antigen by reacting with body-own proteins. Landsteiner and his co-workers furnished the experimental proof of this hypothesis. This theory now is well established and has been generally accepted as the basis of sensitization in contact dermatitis, and also for delayed-type sensitivity in general, especially since Haxthausen³⁸ as well as Landsteiner and Chase⁶¹ reported successful sensitization of the contact-type sensitivity by means of conjugates made up of simple chemicals and proteins. As far as contact dermatitis is concerned, the following appears to be the generally assumed and accepted interpretation: The simple chemical which is not antigenic by itself is called a hapten. It combines with some protein to form a complete antigen which is capable of sensitization. The hapten is considered to be the specific factor, whereas the protein part of the complex antigen appears relegated to the role of conferring antigenicity to the compound and therefore usually is called the "carrier" or "schlepper." There is no doubt that the simple chemical can confer specificity to the complex antigen. However, there is no support for the assumption that the protein is only a "nonspecific carrier molecule." Some experiments carried out several years ago and which will be presented in a later paper had suggested to me that the protein part of the complex antigen may play a rather active and specific role. Also, a survey of the immunological literature on complex antigens indicates that this protein component almost always has a specificity of its own. The hypothesis* on the antigen-antibody reaction in contact dermatitis which is presented in this paper, is based essentially on the assumption that both the hapten and the protein part of the conjugate antigen play a role in regard to specificity and

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*It is with considerable hesitation that I am presenting a hypothesis which contains so much of the speculative. I am fully aware that some parts of the hypothesis are assumptions based on rather scanty experimental evidence, if any. It seems to me that this presentation is justified if it only stimulates more investigation in the large field of antigen formation in delayed-type sensitivity.

The hypothesis presented is based essentially on ideas which are gained from others, and a few which I think are original with me. To all those whose contributions or names should have been mentioned but have been omitted for brevity's sake, or overlooked inadvertently, I offer my sincere apologies.

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reaction. The application of this theory would help to explain some aspects of contact sensitivity as well as other forms of delayed-type sensitivity.

PART I

Presentation of Hypothesis and Its Application

The hypothesis† on the antigen-antibody reaction in contact dermatitis is based on the following six points:

I. The actual antigen in contact dermatitis is a complex of a simple chemical (hapten) with a protein.

II. The protein part of the conjugated antigen in contact dermatitis is not just a more or less non-specific "carrier" to make the complex antigenic but is a specific part of the complex antigen. It will be called "protigen" in the following.

III. (a) The proteins which combine with the hapten to form complex antigens in contact type skin sensitivity are derived from the skin, i.e., epidermis, dermis or its appendages.

(b) The same hapten (simple chemical or polysaccharide) may form several conjugates by combining with different proteins.

IV. The antibodies are produced in the lymphatic tissues. It is postulated that the lymphoid tissue of the skin may also participate in the process of antibody formation.

V. A conjugate may provoke several antibodies. The antibodies in contact dermatitis are directed against either or both the hapten (i.e., the simple chemical) and the "protigen" (i.e., the specifically altered skin protein).

VI. Under certain circumstances the simple chemical which usually unites with a protein to form the conjugate, may only alter some skin protein or proteins into specific antigens without combining with them (autosensitization).

APPLICATION OF THEORY

A theory has a double function: To provide a concept for hitherto unexplained observations, and to stimulate research. Many phenomena of contact dermatitis and delayed sensitivity are still puzzling. The hypothesis presented may help to explain some of them.

†As the so-called "contact-type" sensitivity is just one form of the delayed-type sensitivity, this theory will be more or less applicable to delayed sensitivity in general.

The following terms are used as synonyms in this paper:

1. Immediate, immediate-type or immediate wheal type sensitivity or reaction, urticarial sensitivity, anaphylactic sensitivity, atopic sensitivity.

2. Delayed or delayed-type sensitivity, or reaction, with its two subgroups:

(a) Tuberculin-type sensitivity, or bacterial allergy or papular reaction, or dermal non-atopic sensitivity, or delayed papular type sensitivity.

(b) Eczematous sensitivity, or epidermal sensitivity, or delayed vesicular type sensitivity.

The term contact-type sensitivity is used to indicate either or both types of the delayed type sensitivity.

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Specific Sensitivity of Skin

The most obvious and probably most puzzling phenomenon of contact type sensitivity is the fact that it is confined to the skin. Usually, even in the case of severe sensitivity of the skin, the mucous membranes tolerate the same antigen perfectly well. Chewing of poison ivy leaves probably no longer is the fashion of the day, but I have never seen a reaction in my patients with poison ivy or ragweed dermatitis when they dissolved slowly the antigen, placed on a piece of lump sugar, in their mouth. J. Jadassohn⁵⁰ long ago proved that iodoform was tolerated without reaction in iodoform sensitive patients when inserted into the vagina without contact with the skin. L. Goldman and B. Goldman³¹ have clearly shown the usual lack of correlation of sensitivity of skin and mucous membranes by their patch tests on the mucous membrane; the organ sensitivity may be even so specific that it may be restricted to the lips only, as in Goldman's³⁰ case of cheilitis from penicillin. The theory that the antibody in contact dermatitis is directed both against the simple hapten and skin protein provides an explanation of the phenomenon that sensitivity of the skin and of the mucous membranes are usually independent of each other. In one instance the "protigen" is derived from skin constituents, and therefore the antibody would not necessarily react with an antigen derived from mucous membrane, and vice versa; the occasional double sensitivity of both skin and mucous membranes could be explained by antigen formation in both structures, with subsequent simultaneous appearance of antibodies to both. The possibility also has to be considered that at times there may develop sensitivity to a protein structure common to both skin and mucous membrane.

Characteristic Clinical Picture

Equally interesting, but not as widely recognized, is the fact that certain chemicals produce more or less characteristic clinical pictures. To mention a few examples: poison ivy, and less frequently, weeds, produce a bullous dermatitis; the Chinese primrose usually elicits a severe but superficial dermatitis which clears rapidly in contrast to ragweed dermatitis which shows, almost always, infiltration and lichenification and takes a prolonged course. Sulzberger and Wise reported that in patients who were hypersensitive both to butesin and picric acid, each of these substances seemed to produce an individual, more or less characteristic, pattern. Butesin caused a persistent follicular eruption and deep edema; picric acid, diffuse severe erythema, little edema and many minute non-follicular vesicles. Some chemicals like iodoform (Frei) produce a more superficial dermatitis, others like nickel show mostly a lichenified infiltrated patch. Some contactants produce a diffuse pattern; others, like nail polish, usually produce localized patches. Even the same substance produces different clinical pictures; chromate sensitivity may

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lead to acute vesiculo-bullous, diffuse superficial contact dermatitis or to localized patches of eczema or to nummular eczema-like lesions. These differences, although they may also be due to sensitivity to different determinants of the same antigens, or their mode of contact, appear essentially based on a difference of the actual shock organ. Contact dermatitis is not just a manifestation of epidermal sensitivity. The role of dermal delayed sensitivity, evident by the experiments on guinea pigs, has been stressed in recent years by some clinicians.^{24,40,78} What is less recognized, however, is the fact that these two forms of delayed sensitivity are to some extent independent of each other. (See page 645.)

Our theory is well suited to explain these phenomena. As the protein of the conjugated antigen may be derived from different structures and the antibody reacts both with the hapten and the protigen, antibodies produced by different chemicals may have an affinity for skin in general as well as for specific skin structures. The following scheme may illustrate the application of these postulates and their consequences:

Hapten combined with protein from	Result
Epidermis	Epidermal delayed sensitivity (eczematous contact type sensitivity).
Dermis	Dermal delayed sensitivity. (Tuberculin type sensitivity, "papular sensitivity" (Haxthausen), "dermal non-atopic sensitivity" (Epstein).
Special Structures	
Follicular apparatus	Follicular eruptions
Sweat gland apparatus?	Dysidrotic eruption
Deeper structures	Drug eruptions
Mucous membranes	Contact type dermatitis of mucous membranes

As the same chemical may engender several antibodies also directed against several structures of the skin, the great variety of clinical pictures, even by the same contact allergen, becomes understandable. This specificity of the antibody could also explain the selectivity of certain drug eruptions for special structures of the skin, such as the appendages, and the pigment producing cells.

Characteristic Picture of Trichophytids

One may also extend this concept to haptens in delayed-type microbic sensitivity. It is well known, and has been re-emphasized recently by Peck⁷³ that the follicular trichophytid, the lichen trichophyticus, usually accompanies markedly inflammatory fungus infections of hairy regions such as scalp or beard; while the dyshydrotic eruptions of the hands are usually found associated with dermatophytosis of the feet. There has been no satisfactory explanation of this phenomenon. Peck claims that this is due to differences of the causative fungi, a trichophyton being the cause of the inflammatory follicular ringworm and an epidermophyton responsible for the dermatophytosis of the

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feet. This explanation does not appear tenable any longer. Probably the greatest number of inflammatory ringworm of the scalp (kerion) are caused by one of the fungi of the gypseum group; the main fungus causing dermatophytosis of the feet is trichophyton interdigitale (see Epstein,²⁰ p. 147); this fungus is also a member of the gypseum group.^{20,46} Thus it is actually the same fungus that causes a follicular trichophytid in one instance, and a vesicular one in the other. Our theory can readily explain the situation. In the case of the kerion, or other inflammatory ringworm of the hairy regions, the follicular apparatus is mainly involved, and conjugates apparently formed from some protein of the follicles. This is supported by the observation that a positive trichophytin reaction in follicular inflammatory trichophytosis of scalp or beard may show accentuated involvement of the follicles. In dermatophytosis of the feet, so called epidermophytosis, the lesions are usually vesicular or bullous, and apparently conjugates are formed from other structures, perhaps sweat ducts, or some structures peculiar to soles or palms, but not related to hair follicles. Thus we can expect a follicular trichophytid in the one instance, and a vesicular in the other. It seems likely that in both instances antibodies are also formed directed against other conjugates from proteins of skin in general; thus accounting for the ordinary papular trichophytin reaction usually encountered in both forms of ringworm.

Localized Sensitivity

There are three closely related phenomena in delayed-type sensitivity that so far have not been explained satisfactorily.

1. "Localized sensitivity" is often found in contact dermatitis; I shall mention as an example nail polish dermatitis. It is immaterial here whether such localized sensitivity exists absolutely or whether, as Peck believes, it is a relative affair and what we clinically call by this term means only localized increased sensitivity where the general sensitivity is too low to be manifested by our ordinary tests.

2. Landsteiner and others, studying the spread of sensitization in contact dermatitis, found that when skin islands in guinea pigs were severed from the rest of the skin by cutting out a ring of tissue around them down to the fascia, a sensitizer applied to this localized area as a rule would produce only local sensitivity of this island, but not of the rest of the skin of the treated animal.

3. Patch tests, as well as intradermal microbic tests, often produce a stronger reaction the closer the tests are applied to the site of dermatitis or trichophytosis.⁸⁸ These clinical observations have been confirmed by experimental studies of Haxthausen and of Grolnick.³³

These three phenomena cannot be explained by the accepted concept of sensitization in contact dermatitis, according to which the antibody formation occurs in lymphoid tissue outside of the skin, and the antibodies are

spread entirely through the lymphocytes of the blood. However, the assumption of local formation of antibodies in the lymphoid tissue of the skin would provide a plausible explanation.

This assumption may also explain some phenomena of the so-called flare-ups of old test sites, a problem which has been thoroughly studied and recently reviewed by Grolnick.³³

Cross Sensitivity in Contact Dermatitis

Since R. L. Mayer's⁶⁰ studies on cross sensitivity to substances with quinone structure, this important subject has attracted increased interest. Cross sensitivity usually can be accounted for by the presence of the same immunological determinant, a chemical group or grouping of the original substance or its derivative. This leads to the production of antibodies which will react with various chemicals having the same determinant group. However, there are observations which do not fit this scheme so easily. Perhaps the theory presented here may shed some light on these phenomena. The group pattern of sensitivity for a certain chemical is not always the same; in certain instances there is cross reaction with a certain set of related substances, in other instances with a different set. The assumption that the same chemical may produce more than one conjugated antigen, and that the antigen may produce more than one antibody would furnish a plausible explanation.

There is another observation in cross sensitivity to which Landsteiner and Chase⁶¹ called attention. They reported that picryl chloride is a strong sensitizer, but picric acid a poor one. In regard to cross reactions they stated that "guinea pigs sensitized with picric acid gave cross reactions with picryl chloride, and animals intensely treated on the skin with large quantities of picryl chloride showed some sensitivity against picric acid, perhaps by liberation of the latter substance in the skin."

Perhaps a different view can be given to explain both the fact that picric acid is a poor sensitizer and that animals sensitive to picryl chloride usually did not cross-react with picric acid. From Landsteiner and Chase's⁶⁰ studies with picryl conjugates, it seems evident that the sensitivity to picryl chloride is due to the picryl radical and not to the chlorine atom, because the latter is eliminated in the process of conjugation. Picryl chloride is a rather active chemical and, according to Landsteiner, this makes picryl chloride a stronger sensitizer than the chemically less active picric acid. If we accept the postulate of a more complex mechanism of the formation of natural conjugates in contact sensitization, we may assume that picric acid too, by some more intricate mechanism, may form conjugates by means of the picryl radical. However, this probably happens only under certain circumstances and/or to a lesser degree. In this case it would be understandable that animals sensitized to picric acid always cross-react with picryl chloride, because the latter is always ready to furnish the needed picryl radical. However, when sensitivity has been engendered by the

readily reacting picryl chloride, the application of picric acid may not produce enough picryl radicals to elicit a reaction, unless there is an unusually high degree of hypersensitivity. From these observations one may formulate a sort of a law: If sensitivity to different chemicals is due to the same radical, individuals sensitized by a chemical which is less reactive always cross-react with those other chemicals that free the radical more easily, but sensitization to a reactive member of the group does not necessarily produce cross sensitivity to those other group members that give up the radical less easily. Such viewpoint seems supported by Rostenberg and Perkins⁸⁰ work on nickel and cobalt sensitivity. This assumption might also explain some discrepancies in "para" sensitivity.

There are other unsolved problems of cross sensitivity; I shall mention as examples the cross sensitivity to heavy metals, and the inconsistencies found by Lamb and Lain⁸⁷ in their studies on cross sensitivity to gasoline dyes. Part of the latter might be explained on the basis of the "law of reactivity" discussed above.

The cross sensitivity found between nickel and cobalt has been explained by the chemical similarities of these elements³² as they belong to the same subgroup—iron, nickel, cobalt—in Mendeleyev's periodic system of elements. This would form a parallel to what is known about halogenated proteins; antibodies are directed against the newly formed compound, not against the particular halogen used. Thus animals sensitized with iodinated proteins cross-reacted with brominated proteins.

However, the cross reactions to metals seem to go beyond the boundary of chemical affinity. In many instances of sensitivity of humans to nickel, there exists also sensitivity to copper. Copper does not belong to the iron-nickel-cobalt group, but rather to a subgroup that also contains gold, silver.³² One may think here of the possibility that the hapten combines with the skin protein in such a way that the specificity of the conjugate is due to the protein part ("protigen") and not the hapten component, or of the possibility that the chemical only alters the body's own protein without combining with it. As the same chemical may produce more than one type of antigen and more than one form of antibody, one can only guess at the many and varied possibilities which may underlie cross sensitivity to a certain substance. One word of warning in regard to experiences of cross sensitivity in humans is in order. Whether we are really dealing with "cross sensitivity" in all these instances is not sure. In anaphylactic sensitivity, cross sensitivity can be established by exhaustion of precipitins, et cetera, whereas in contact dermatitis cross sensitization is considered likely when two or more substances with chemical similarities produce reactions on the same patient. It is possible that some cases of "cross sensitivity," e.g., nickel and copper, actually are only instances of simultaneous sensitization to two chemicals which are quite often alloyed. The final answer to these problems may be found in studies of cross sensitivity in

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experimental sensitization of animals with pure chemicals, rather than in an analysis of cross sensitivity as found in patients suffering from contact dermatitis.

Role of Autosensitization in Contact Dermatitis

If the assumption is correct that simple chemicals may produce antigens from the body's own proteins ("protigens") without combining with them, then autosensitization would appear to play a far greater role in contact dermatitis than is usually assumed. Autosensitization or sensitization to a "protigen" may also be a factor, in certain id-like eruptions (allergids) as well as in the pathogenesis of erythroderma.

ALLERGIDS

The word "allergid" is used as an over-all term for the so-called "ids" or id-like eruptions, regardless whether they are caused by micro-organisms or their products (microbids) or by chemicals or by a combination of the two. It is generally assumed that these allergids are an expression of generalized allergy to the causative microbic or chemical antigen. That such a mechanism is a factor, perhaps the main factor, in the causation of allergids, there can be little doubt. But this does not seem to be the whole story; it is well known that the allergid in contact dermatitis, especially from drugs, is clinically different from the original dermatitis. Often the allergid appears as a diffuse papular or papulo-macular eruption which may or may not later on turn into an eczematous process. One may attribute this form of reaction solely to the hematogenous spread of the eruption; however, when these patients are tested with the drug which apparently caused the dermatitis, a patch test may be negative. I have seen this in cases of allergids following the application of sulfathiazole and rivanol to infectious eczemas of the legs or stasis ulcers, where the sequence of events left little doubt as to the etiological role of that drug. At times there is no, or remarkably little, irritation at the original site of the application of the causative ointment; or the flare-up here may occur only days after the allergid appeared on the arms or legs. These cases obviously lend themselves to an explanation on an autosensitization basis.*

The similarity of this id-like eruption in contact dermatitis with the maculo-papular dermatophytids is so striking that one cannot help but consider also the possible mechanism of trichophytids. Most of them are apparently due to a sensitization to some products of the fungus and a complex antigen is probably formed similar to that in contact dermatitis. In the presence of a follicular or vesicular dermatophytid, the trichophytin

*A negative patch test does not always exclude sensitivity to that particular drug. I am referring to an observation of mine where the application of rivanol caused a severe allergid. A patch test with the same drug was negative, but an intradermal test showed a severe delayed reaction to rivanol. This, however, indicates only that this patient's contact dermatitis was based on dermal rather than epidermal sensitivity; the allergid may still have been an expression of autosensitization, because he may have been sensitized both to the chemical and the protigen.

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reaction—at least in my experience—is always positive. But there exists also a different form of a generalized dermatophytid, occurring usually in children or younger adults, which originates as a papular allergid of the extremities. In these cases the trichophyton reaction not infrequently has been found negative, even during the eruptive stage. This has been explained as an exhaustion of sessile antibodies, a refractory state; however, this seems rather unlikely; as Rostenberg⁷⁹ (p. 179), states, “it is difficult to conceive of a cutaneous eruption predicated on an allergic hypersensitivity to fungous products and yet have the individual fail to react to an extract of these fungous products when tested elsewhere on the body.” In this type of allergid which so often follows irritation of the primary dermatophytosis, especially from too intensive treatment, the skin may be sensitized to a protigen. This form of allergid then is rather an expression of autosensitization, than a true trichophytid.† If this interpretation is correct, a negative trichophytin reaction in some of these cases can be well understood.

ERYTHRODERMA

Autosensitization may also be a factor in that peculiar condition called erythroderma, which may follow various forms of dermatitis, as well as psoriasis or lymphoblastomas. In the former two conditions, the erythroderma can often be traced to treatment too strong or irritating for that particular stage. The role of sensitization is obvious in erythroderma following a dermatitis. Microbic sensitization seems likely as a factor in psoriasis, and the term “leukemid” suggests the assumption of sensitization phenomena in lymphoblastomas.

At present one can only speculate why the allergid usually is a more transient phenomenon, whereas the erythroderma is such an eminently chronic process often lasting many months or even years, and interrupted or terminated earlier usually only by corticotropin or adrenal steroids. That these erythrodermas are maintained by a continuous action of antigen may be supposed in cases of arsenical erythroderma; but it is difficult to explain an erythroderma following ultraviolet treatment of psoriasis on this basis. One might assume that in these cases of erythroderma the infectious process which initiated the autosensitization, continues and produces protigens through the bacterial flora of the erythrodermatic skin. Perhaps it is more likely that an overwhelming sensitivity to normal skin has developed. It seems to me cases of true erythroderma deserve a study from the autosensitization angle.

†This may also apply to certain vesicular eruptions of the hands associated with dermatophytosis of the feet, but with negative trichophytin reaction. Such a negative reaction now is considered proof that these cases are not dermatophytids, but of other origin. Some probably are connected with food or drug allergy (“endogenous eczema” of Vickers); still the possibility must be considered that even in some of these cases the original dermatophytosis may play a part by acting as an “adjuvant,” enhancing delayed-type sensitivity to a different agent.

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PART II

Review of Immunological Background

Before presenting the supporting evidence for the six postulates (p. 634), I shall review some aspects of sensitization which appear relevant for the discussion, such as the principal forms of skin sensitivity, complex antigens, formation of antibodies and autosensitization.

PRINCIPAL FORMS OF SKIN SENSITIVITY IN DERMATITIS

There are two main forms of allergic sensitivity: the immediate-type and the delayed-type sensitivity. A summary of their salient features of distinction may be found in papers by Epstein²⁸ and Rostenberg.⁷⁹ Recent studies have added more differences, especially in their response to antihistamines (see Epstein and Paulson).²⁸ The immediate-type sensitivity includes anaphylactic as well as atopic sensitivity. These two forms, though different in some respects, are closely related (see also Rostenberg⁷⁹) and not worlds apart as formerly thought and still assumed by some (Boyd,⁶ p. 326), (Reddin⁷⁶).

The delayed type sensitivity includes both the so-called tuberculin-type and the eczematous-type sensitivity. It is still customary to distinguish between these two forms of sensitivity, as if they were different in principle. However, several authors (Haxthausen,⁴⁰ Rostenberg,⁷⁹ Epstein²³) have expressly recognized the close relationship between, if not identity of, these two forms of delayed sensitivity. It is interesting to note that Landsteiner as well as Doerr,¹⁶ apparently always recognized this identity because they never seemed to bother about the distinction between these two forms of delayed skin sensitivity. The essential difference appears one of shock organs; in the former, some dermal structures, in the latter—most likely—the epidermis. In actual contact dermatitis both forms are often, perhaps usually, encountered, though the dermal sensitivity has been largely neglected.

In spite of the many fundamental differences between the immediate and delayed types of allergic sensitivity, the supporting evidence presented for this hypothesis about delayed-type sensitivity, will be largely based on observations on immediate-type sensitivity. The reason for this is that the experimental work on antigens and antibodies has been done essentially with regard to anaphylactic sensitivity, whereas the experimental work on antibodies and passive transfer in eczematous as well as tuberculin type is still very limited, especially in humans (see Lawrence,⁶⁷ Baer and Sulzberger,² Wesslen,⁹⁸ Haxthausen³⁷). Therefore one has to apply principles of general immunology in establishing a working hypothesis about the antigens in contact dermatitis. However, it is obvious that observations made in regard to immediate-type sensitivity may not necessarily apply to delayed-type sensitivity.

COMPLEX ANTIGENS

The term antigen* covers two functions—(1) the capacity to produce antibodies; (2) the capacity to react with or neutralize antibodies.** Full

*As Doerr¹⁶ (p. 330, 331) emphasizes, "antigen," like "toxin," is a functional term, not an absolute concept on the same level as "proteins" or "carbohydrates." "The term antigen characterizes just one of the 'reaction forms' of the organism to the invasion of foreign elements into its biochemical system. In other words, in that organism where the antigen originates and persists, the antigen is not an antigen, but a substance which, like other substances, participates in the physiological processes, is synthesized, metabolized and used."

**See following page for footnote.

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antigens possess both qualities. Partial antigens, or haptens, possess only the second attribute, and become antigenic only after they have combined in some way with proteins or certain other high molecular substances. A schematic presentation of antigens and their mode of action is given in Table I.

TABLE I.

Type of Antigen	Mode of Antigen Formation
A. Full Antigens	
1. Heterologous proteins and other high molecular compounds.	Primarily antigenic.
2. Altered homologous proteins ("proteins"). The substances from which they are derived are not antigenic for the same species; however, they may react with antibodies formed by the altered antigen.	Alteration by external or internal influences: 1. Microbic Toxins (kidney sensitizing, skin sensitizing antigens). (Proven) 2. Physical agents: Ultraviolet rays in urticaria photogenica. Cold in cold urticaria. (Proven) 3. Chemicals (not proven as yet), but assumed by several authors.
3. Altered heterologous proteins.	Alteration due to physical or chemical action
B. Partial Antigens (Haptens)	
1. Simple chemicals. 2. Microbic polysaccharides. 3. Low molecular weight carbohydrates.	Combination with proteins or perhaps other compounds of high molecular weight necessary to attain antigenicity. However, hapten alone capable of neutralizing antibodies directed towards the complex antigen, and apparently capable of eliciting reactions in sensitized organisms.

We are here concerned with the partial antigens which require combination with other substances to become fully antigenic. The resulting antigen is called a complex antigen. We do not know how these antigens are formed *in vivo*. From the *in vitro* experiments and other considerations, several ways of formation of such complex antigens are assumed.^{6,16,22,58} Landsteiner⁵⁸ distinguished chemically active and inactive haptens. He had demonstrated a parallelism between the chemical activity and the sensitizing power of certain substances. The importance of the chemical activity of a hapten is also supported by the fact (Miescher) that a certain concentration of a chemical (e.g., neoarsphenamine) is needed to produce contact-type sensitization. In these instances of chemically active haptens, the formation of a complex antigen may be readily explained on the basis of a chemical reaction; this may occur in two ways³²:

1. The hapten and protein form a chemical compound, either directly (e.g., dinitrochlorobenzene) or after some transformation within the organism (e.g., paraphenylenediamine).

****One might mention here that Marrack⁶⁸ distinguishes two stages in an immunity reaction: "(a) specific combination of the 'determinant groups' with antibody, "(b) secondary reaction-precipitation, agglutination, et cetera." This distinction is based on the fact that the union between the antigen and antibody does not always produce a visible effect. This hapten-antibody combination without visible effect might be truly called a "silent" reaction, somewhat different from the way Popper⁷⁵ uses the term "silent, asymptomatic allergy."**

There is no reason why these two stages of immunologic or allergic reaction should not also occur in contact dermatitis. Thus, in the delayed type sensitivity we may also expect different effects from the union between complete antigens, or part of the antigen and the antibody.

2. The combination of hapten and protein is due to adsorption rather than a strong chemical bond. ("Mixtures," "combination antigens").

Modern chemistry, however, no longer draws a sharp line between chemical bonds and adsorption.

Even in the presence of chemically active substances the actual *in vivo* formation may be more complicated than this scheme indicates. But as Landsteiner has pointed out, certain chemicals are sensitizers but are not chemically active. In some of these cases, it seems fair to assume that the original substance may normally be changed within the organism into a chemically active compound. Even if this explanation should be found correct for the simple chemicals of contact dermatitis, it hardly would apply to those microbic polysaccharides which by themselves are not capable of sensitizing the organism. In these instances we are apparently dealing with more complicated processes. One of these is sensitization by the means of the so-called adjuvants. I am referring especially to what is called the "Dienes effect"; by injecting egg-white into a tuberculous focus, Dienes was able to produce delayed type sensitivity to egg-white. Modifications of this technique, especially employing killed tubercle bacilli, have later been used successfully. In this way antigens will become effective which, by themselves, usually do not produce delayed type sensitivity, such as proteins; or which, by themselves, cannot elicit delayed type sensitivity such as certain polysaccharides of microbic origin. Landsteiner and Chase⁶⁰ were also able to produce skin sensitivity to simple chemicals as well as to artificial conjugates by peritoneal injection with the aid of killed tubercle bacilli. There are also other "adjuvants" which help to induce delayed type sensitization.

Clinical experience with burns⁹³ and other clinical observations indicated to Landsteiner and Di Somma⁶³ that irritation of the skin aids the development of eczematous sensitization. These authors demonstrated experimentally sensitization to picric acid was aided when the skin was previously irritated by cantharidin. That bacterial infections may serve as adjuvants in sensitization to drugs is suggested by Rostenberg⁷⁹ (p. 199). The mechanism by which the adjuvants work is not known. Waksman and Morrison,⁹⁷ in their work on tuberculin type sensitivity to spinal cord antigens, recently have discussed some of the factors involved. At any rate, the experimental work with adjuvants suggests a more complex way of antigen formation than just a simple chemical reaction between a hapten and a protein.* More complex mechanisms of antigen formation are also supported by the experiments of Haurowitz and Crampton³⁶ who proved that the fixation of the antigen to the cytoplasmic granules *in vivo* is not brought about by simple adsorption, but by some other mechanisms, because it cannot be achieved *in vitro*. Analogies with the antigen formation in physical allergy also suggest that this is not just a simple chemical reaction between substances in a test tube, but a more complicated process. In photoallergy to sulfanilamide²¹ it has been shown that the sensitized person reacted to ultraviolet irradiation of the site where sulfanilamide had been injected, whereas sulfanilamide irradiated *in vitro* by the same rays failed to produce a reaction when injected. One has also to consider the possibility that the capacity of different persons to form conjugated antigens as well as that to create the hypothetical protigens may vary as much as their

*The complexity of the process of sensitization in contact dermatitis is also suggested by the strange blocking effect of dermal sensitization by preceding or concomitant intravenous or oral application of the same chemical.^{11,86}

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ability to form antibodies. In this way the same contact may be sufficient to produce a conjugated antigen or a protigen in one instance, but may fail to do so in another. A constitutional factor, or a peculiar genetic predisposition to sensitization in contact dermatitis, long suspected by clinicians, has been suggested by experiments by Landsteiner,⁵⁸ Sulzberger and Rostenberg. Sulzberger and Rostenberg⁹² demonstrated an increased susceptibility to contact type sensitization in individuals with contact dermatitis. Chase⁹ was able to breed guinea pigs especially prone to contact type sensitivity. What this constitutional factor is remains unknown. Perhaps it is related to the ability to develop antibodies. However, if we realize that patients with contact dermatitis are not only more easily sensitized to contact allergens, but also have a lower skin tolerance to primary irritants,⁵⁴ one wonders whether this constitutional factor may not be just as well connected with a greater capacity for the formation of complex antigens.

There is some evidence to support this. It is known, for instance, that in different individuals nickel may produce either epidermal sensitivity, or dermal sensitivity or both. Unpublished studies of mine have shown that in the majority of cases of nickel sensitivity in human beings, one is able to demonstrate both an epidermal and dermal sensitivity, as indicated by their response to patch and intradermal tests. However, in some instances, there exists only a dermal sensitivity,⁴ whereas in others, apparently very rare ones, only epidermal sensitivity can be demonstrated. Moreover, epidermal and dermal sensitivity in different patients who are sensitive both ways, does not parallel each other; some persons exhibit a high epidermal combined with low dermal sensitivity, and vice versa. It would be strange to assume that these people differ in their capacity to form antibodies to an antigen which appears formed in one instance with proteins from the epidermis, in the other from the dermis. Rather, it supports the viewpoint that they differ in their capacity to develop complex antigens. In this respect I have been impressed by a personal experience of mine. In the course of many years I have submitted myself as a control hundreds of times for patch tests; I have never developed epidermal sensitivity, although not infrequently irritating concentrations were used; I have never suffered from contact dermatitis, nor have my dermatophytids ever assumed a dermatitis-like character, over a period of twenty-five years. On the other hand, I seem to have a great capacity to dermal sensitivity. In the few instances when I have experimented on my skin with intradermal injections of simple chemicals (gold, penicillin, sulfanilamide plus light). I have always developed a tuberculin type sensitivity, and following the first injection at that.

ANTIBODY FORMATION

It is now generally assumed, and well supported by facts, that antibodies are modified gamma globulins and that their production takes place, at least in part,¹⁵ in the reticulo-endothelial system, notably lymph nodes and spleen, also bone marrow and liver. There is, however, no agreement as to how antibodies are formed. Antibody formation often continues for many years, although the antigen apparently is destroyed or eliminated rather rapidly. Antibody production must go on because the antibodies, like the gamma globulins from which they are derived, have only a life span of a few weeks. The question then is how is antibody formation kept up after the antigen has been eliminated. There are two main theories.

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Autonomous antibody formation (anamnesic reaction).—The antigen acts as a stimulus for the production of antigens, and this process becomes autonomous and persists even after the antigen has been eliminated.^{8,16} This theory is based on the behavior of particulate antigens which are destroyed within a short time after injection. However, as Haurowitz points out, destruction of the particle does not necessarily mean that the antigenic molecules of the particle are destroyed.

The theory of persistence of the antigen.—It is thought by some that the intact antigen or some antigenic fraction or fragments may be stored in the antibody producing organs, and there serve as a pattern or "template" for the continued formation of antibodies. Haurowitz defends his theory that the long persistence of antibody formation and the long duration of immunity are due to antigen retained at the sites of antibody formation. Recent experiments by Haurowitz and Crampton³⁶ with I-131 Iodo-ovalbumin, as well as the findings of others who used pneumococcal polysaccharides, serum globulins, or azoproteins, indicate that all these antigens persist in injected animals for a very long time.

What is known about delayed-type sensitivity does not permit taking sides in this controversy. However, the facts available so far indicate a great similarity to the conditions in whealing sensitivity. The antibodies are shortlived^{39,62}; but production of antibodies continues as shown by Haxthausen's⁴¹ recent experiments. It is also known that contact type sensitivity may persist for many years, even in the absence of renewed contact.⁵³ Furthermore, Grolnick³³ has shown that the antigen in contact dermatitis may persist in the skin far longer than previously assumed.

ANTIBODY FORMATION IN DELAYED TYPE SENSITIZATION OF THE SKIN

The hapten, contacting the skin, combines with a protein to form a complex antigen. This antigen is carried by the deeper lymphatics to the lymph nodes and other antibody producing structures. Here the antibodies become attached to the lymphocytes and are carried by them through the blood stream to the skin. There are no free antibodies demonstrable in the plasma. How the antibodies are transferred from the lymphocytes to the skin is not known.

The antibody in delayed type sensitivity, both tuberculin type and contact type, has been demonstrated but recently. Landsteiner and Chase's^{60,61} experimental work in animals about the cellular transfer of the antibodies has been confirmed, also on human beings. Delayed type sensitivity has been transferred passively in guinea pigs by intraperitoneal injection of viable lymphocytes. Lawrence⁶⁷ was able to transfer passively on humans generalized cutaneous streptococcal sensitivity of the delayed type by means of intradermal injection of viable leukocytes obtained from streptococcus positive human donors. The antibody apparently is transferred through viable lymphocytes. Haxthausen,⁴¹ Baer and Sulzberger,² as well as Baer, Serri and Kirman,¹ were not able to transfer passively eczematous allergic sensitivity by intradermal injection of white cell suspensions. Hagerman³⁴ believes that the hypersensitivity in contact dermatitis cannot be induced by injection of the lymphocytes directly into the skin; but as Lawrence's⁶⁷ work demonstrates that bacterial delayed type sensitivity can be transferred by the intradermal route, the failure, so far, to transfer by this method sensitivity to simple chemicals may be due rather to technical

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or quantitative difficulties. Anyway, the experimental work of Haxthausen¹¹ leaves no doubt that the lymphocytes are the carriers of the antibodies in contact type sensitivity. Besides transferring delayed type sensitivity, the lymphocytes of sensitized human donors apparently also facilitate active sensitization of the recipient.^{2,67}

AUTOSENSITIZATION

The status and theory of autosenitization* has been reviewed not long ago by Templeton, Lunsford and Allington,⁹⁴ who, like Cormia,¹² stressed the importance of this concept for eczematous processes, and more recently by Esplin and Cormia.²⁹ As far as I can see, the first one to discuss sensitization to altered body protein, as a cause of dermatitis was J. Jadassohn,⁴⁹ when he suggested this possibility as explanation for physical allergies. The broader concept of autosenitization originated with Whitfield.¹⁰⁰ Ingram⁴⁸ expressed the thought that the etiology of eczema (i.e., contact dermatitis) is in every case "a background of sensitiveness, an external provocation and a degree of autosenitization once the eruption is in being." Sulzberger⁸⁹ stated his hypothesis on autosenitization as follows: "1) Alteration and liberation of organ specific antigenic excitants, created within the body from autochthonous organ tissues by various infective or non-infective agents. 2) Formation of organ-specific antibodies to these antigens. 3) The continuous or intermittent damaging effect of these antibodies upon the respective living organs *in situ*."

Simon⁸³ recently reviewed his extensive studies on allergy to human dander. He concludes from recent experiments that the antigen is derived from the epidermis itself. Esplin and Cormia²⁹ showed that 50 per cent of their twenty-four cases of autosenitization dermatitis gave immediate reactions, and again 50 per cent delayed reactions to aqueous autogenous scale extracts. The primary reaction type of these cases was contact dermatitis in eleven, and in ten further cases eczemas which can be considered partly of infectious origin (stasis, seborrheic, nummular), and in two instances dermatophytosis. The allergen in Simon's,⁸³ as well as in Esplin and Cormia's²⁹ experiments, is contained in the water soluble fraction of skin, and perhaps is identical. The fact that Simon was able to elicit skin reactions to apparently unaltered body-own constituents does not mean that the sensitivity originally was caused by them. Body-own proteins, can elicit antibodies only after they have been altered into a "foreign" substance for the organism,** but it is known that antibodies formed in response to these changed body-own constituents may react at times not only with the altered but also with the original unchanged proteins. If this applies also to skin we may distinguish in this respect a form of autosenitization directed only to altered body-own proteins and another one directed to the original protein.

INTERACTION OF PHYSICAL ALLERGY, AUTOSENSITIZATION, CONTACT AND BACTERIAL SENSITIVITY

That autosenitization plays a part in actinic allergy, has been emphasized

*Autosenitization or sensitization to body-own constituents may be both of the immediate wheal and the delayed inflammatory type. The discussion here is restricted essentially to the latter.

**However, unaltered body-own proteins may be antigenic in the same species, as shown by Cumley and Irwin¹³; but in their experiments the serum was antigenic only in other individuals of the same species, similar to the corpuscular antigens of the blood groups.

recently by Bernstein,⁵ Sulzberger and Baer⁹⁰ had concluded from the passive transfer experiment in sunlight urticaria that the antigen ought to be an altered body-own substance. The interaction of contact sensitivity and physical allergy has been proven in cases of photoallergy to sulfanilamide^{7,21} as well as to the oil of persian lime.⁸¹ In both instances the combined effect of a simple chemical plus ultraviolet are necessary to produce a reaction. A more complex interaction of photoallergy, contact sensitivity and autosensitization becomes apparent from Juon's⁹² case. His patient became sensitized to light during the course of antiluetic therapy, with neosalvarsan and mercury. This patient also had a contact sensitivity to these drugs alone. At first his sun sensitivity depended on the concomitant presence of these chemicals and light. But later on, sunlight alone was capable of eliciting the dermatitis, apparently an expression of some form of autosensitization.

The interplay between physical allergy and the influence of bacterial toxins is suggested by certain clinical observations. Stokes and Galloway⁸⁵ called attention to the interrelation between light sensitivity and pyogenic infections. Barber⁸ and his co-workers always stressed the role of intestinal dysbacteria in polymorphous light eruptions. Urbach and Shay⁹³ reported a case of severe light hypersensitivity which cleared up after removal of an infected gall bladder. The frequent association of prurigo estivalis and lymphopathia venerea has been shown by Sonck.⁸⁴ Dainow¹⁴ reported recently the recovery of three cases of polymorphous light eruption following treatment with gantrisin. Perry and I⁷⁴ observed a patient with eczema of the hands with sun sensitivity of many years standing. The patient exhibited severe delayed reactions to staphylococcic toxoid. The eczema and sun sensitivity disappeared after desensitization to staphylococcic toxoid, and treatment with testosterone. The mechanism of this relationship between sun sensitivity and infection is not known. The older explanation on the basis of intestinal production of porphyrins, still maintained by Dainow, seems untenable. Among others, Epstein^{22,26} has shown that there is no proof that porphyrins are the light sensitizers in this condition. I am rather inclined to think the relationship comes via sensitization to bacteria or bacterial products. While there is no proof for this assumption either, there exists a sort of a parallel situation in contact dermatitis. Patients with bacterial eczemas become far more easily sensitized to externally applied drugs than any other group of dermatoses²⁷; in my experience even more easily than patients with plain contact dermatitis. Haxthausen⁹⁷ many years ago pointed out the high rate of such sensitization in seborrheic dermatitis. The explanation of these phenomena in contact as well as in physical allergy by a synergistic action of these factors with bacterial products is well supported by the experimental production of autosensitization by the combined use of bacterial toxins and proteins, mentioned on page 654. It seems likely that in polymorphous light eruption (prurigo estivalis) the photoallergen is produced from normal skin by the action of, or in combination with, a toxin or other bacterial antigen.⁴

IMMUNOLOGIC DATA WHICH SUPPORT THE SIX POINTS OF THE HYPOTHESIS

I. *The Actual Antigen in Contact Dermatitis is a Complex of the Simple Chemical (Hapten) with a Protein*

This is generally accepted and so well founded, especially by the work

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of Landsteiner and his co-workers, that there is no need to quote the more than ample evidence.

II. *The Protein Part of the Complex Antigen is not just a "Carrier" to Make the Complex Antigenic, but is a Specific Part of the Antigen ("Protigen")*

Immunologists^{6,16,58} have always stressed that the protein part ("protigen") of a complex antigen has a specificity of its own, but this has been neglected in contact type and delayed type sensitivity. Even following a chemical process as drastic as halogenation or nitration of proteins, the species specificity of the resulting compound antigens is not entirely destroyed (Boyd,⁶ p. 97; Wormall¹⁰²). Also diazotized or other conjugated antigens, will produce antibodies directed toward the hapten and toward the protein fraction. It was only by the use of certain artifices that Landsteiner⁵⁸ (p. 158) could definitely establish the specific reactivity of haptenic groups in artificial compound antigens. Only under proper conditions, the specificity is directed towards the hapten only and is independent of the protein portion of the antigen. However, the hapten is by no means the only immunologic determinant in complex antigens. (See Table II.)

TABLE II. IMMUNOLOGICAL DETERMINANTS IN COMPLEX ANTIGENS

("Conjugated antigens," "Substitution antigens," "Combination antigens (mixtures)")	
1.	Newly formed compound
2.	Hapten only
3.	Both hapten and protein are specific
	a. Antibodies against either part are independent of each other.
	b. Antibody is directed simultaneously towards the hapten and protein part ("protigen").
4.	Protein part ("protigen") is the immunological determinant and not the the hapten.

If the protein part of the conjugated antigen is highly specific in anaphylactic sensitivity, then there is no reason why this should not also apply to delayed type sensitivity. For this specific protein part of the antigen, I am using the term "protigen," because the term "carrier" appears inaccurate. A term is needed that emphasizes the specific role of this antigenic protein ("protigen"). The specificity of this protigen is by no means necessarily, or only, the same as that of the original protein from which it was derived. According to Boyd⁶ (p. 130), almost any decided chemical change in a protein alters its specificity.

III. *(a) The Proteins which Combine with the Hapten to Form a Complex Antigen in Delayed Type Skin Sensitivity are Derived from the Skin, i.e., Epidermis, Dermis or its Appendages*

Originally it was thought that contact with the skin was necessary to produce contact-type sensitivity experimentally; Landsteiner, and his co-workers, proposed the idea that such contact was not essential. Rostenberg,⁷⁸ although thinking that protein conjugates in contact dermatitis are formed ordinarily in the epidermocutis, does not believe that this is an essential requirement.

The following will show that the existing observations do not necessarily contradict our assumption that the conjugate in delayed skin sensitivity is formed by proteins from various skin structures.

A special role of the skin in the establishment of delayed type skin

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sensitivity has been assumed for a long time. This point has been emphasized again by Grolnick;³³ as he puts it: "The skin is not merely the end point, it is also the medium."

It was formerly thought that the hapten had to come into direct contact with the skin to effect sensitization of the contact type. In the light of the theory of conjugated antigens, this could well mean that the proteins with which the skin combines are derived from the skin or its appendages. Such a view appeared supported by early experiments which indicated that sensitization of the contact type could be accomplished only by epidermal or intradermal application of the simple chemical.^{63,67} However, clinical experience and later experiments contradicted this assumption.

Experience with contact-type sensitivity induced by oral use of aspirin and quinine, and also following intravenous arsphenamine therapy, has always suggested that sensitivity of the skin may be achieved by any route of application. More recent experiments by Haxthausen,³⁸ Seeberg,⁸² and Landsteiner and Chase⁶⁰ demonstrated clearly that skin sensitization can also be achieved by subcutaneous, intramuscular, or intraperitoneal injections. Therefore there can be no doubt any longer that the skin does not have to be the primary organ of entrance for achieving contact type sensitivity. The divergent findings of older and more recent experiments can be reconciled by the observation of Haxthausen and others that larger amounts of the antigen are needed for those methods of sensitization where the antigen does not come primarily in contact with the skin.

If this observation is correct that larger amounts of antigen are necessary for extracutaneous sensitization, it would speak in favor of the assumption that contact with skin tissue is necessary for delayed type sensitization of the skin, and that the efficacy of extracutaneous modes of sensitization is due to the indirect secondary contact with the skin. It is well known from clinical experience that internally and parenterally absorbed antigens may reach the skin and produce in this way a contact type dermatitis or other forms of dermatitis based on delayed-type sensitivity. I shall mention here only the flare-up of old sites of poison ivy dermatitis following ingestion or injection of poison ivy extracts. Such observations, however, only indicate that amounts of antigen sufficient to elicit a reaction in sensitized persons may reach the skin when the antigen is administered internally.

There are, however, as far as I can see, several experiments which seem difficult to reconcile with the assumption that the protein of the complex antigen in contact dermatitis is derived from skin structures. Landsteiner and his coworkers were able to sensitize by injecting the hapten into the peritoneal cavity. In Seeberg's⁸² experiments injection of dinitrochlorobenzene into lymph nodes was equally effective as intradermal injection in producing delayed skin sensitivity, and superior to the subcutaneous and other routes. There may be a common denominator of the two phenomena, because the peritoneal sac drains into lymph nodes, and injection of antigens into the peritoneum therefore may mean sensitization via lymph nodes. It is recognized that the lymph nodes, like other organs of the reticulo-endothelial system, are a primary site of antibody formation. But how could the hapten in these instances combine with skin protein? One may suggest the possibility that this may occur within the lymph nodes; Seeberg injected the antigen into lymph nodes which received drainage from skin; according to Drinker and Yoffey,¹⁷ 80 per cent of the drainage from the peritoneal sac goes to the intercostal nodes. These

are nodes which apparently also receive drainage from the skin; therefore, the assumption that the hapten reaching the lymph nodes either by lymphatic drainage or by direct injection, meets and combines there with skin proteins drained from the skin may not be too far-fetched. After all, foreign particles injected into the skin, malignant cells, are known to be drained by the lymph nodes. It is now recognized that the antigen in contact dermatitis spreads through the deeper lymphatics, and not through the blood circulation (Landsteiner); therefore, proteins or particles from disintegrating skin cells probably do the same.

The most serious objection to the assumption that a skin protein is needed for the formation of a complex antigen in contact dermatitis comes from the work of Haxthausen⁵⁸ and Landsteiner and Chase,⁶¹ who apparently were able to produce delayed type sensitivity of the skin by conjugates which contained proteins not derived from the skin. However, the interpretation of these experiments is debatable. Haxthausen's conjugate, according to Landsteiner and Chase,⁶¹ contained considerable quantities of the free hapten. Although Landsteiner and Chase's⁶¹ experiments were carried out with pure conjugates without any traces of the free antigen, their experiments cannot be considered convincing proof that the conjugate is responsible for the sensitization. The authors themselves ponder the possibility, that the picryl conjugates may be split in the body, and that some split-off simple chemical may be the cause of the sensitization. Although these authors discard this possibility, there are good arguments against the conclusion that the sensitization was due to the intact conjugate. The main objection seems this: If their conjugates were really the sensitizing antigen then one would expect that the intradermal injection of the conjugate would promote sensitization. Yet Landsteiner and Chase⁵⁹ report that skin sensitivity of the delayed type could not be induced this way. There is, apparently, no definite report that intradermal injection of a conjugate produced a contact type reaction in sensitized animals. Klopstock and Selzer⁵⁵ were unable to produce such reactions with diazonium compounds. Kooij and van Vloten⁵⁶ also failed to produce skin reactions by intracutaneous injections of a sulfanilamide azoprotein (derived from human serum) in patients with hypersensitivity to sulfanilamide. Landsteiner and Jacobs⁶⁴ believed that they observed reactions of the type of "contact dermatitis," because "injected into the skin, the acylated protein produces an immediate flare and wheal, followed in stronger concentrations by large pinkish edematous reactions on the next day." However, such a reaction does not correspond to the inflammatory response of contact dermatitis. It is known from clinical experience and also evident from experiments of Chase¹⁰ that severe urticarial (anaphylactic) reactions of the skin may last for twenty-four hours or more. The reactions observed by Landsteiner and Jacobs appear more likely prolonged anaphylactic reactions and not truly delayed type reactions.

III. (b) There is no reason to assume that only one conjugated antigen may be formed by the effect of a simple chemical on constituents of the skin. It is known that a chemical may cause sensitization in more than one way; even so simple a chemical as iodoform may produce sensitivity either by its iodine or by its methyl group. Therefore, the simple chemical, the hapten, may give rise to more than one antigen. Neither is it demonstrated or even likely that chemicals with different affinities should cause the same changes in the proteins they combine with. If we add to this the fact that the same antigen may give rise to more than one antibody, directed

against different structures, then we realize the possibility of a multitude of combinations. This may apply equally to the protein part of the complex antigen, i.e., the same protigen may also produce different antibodies, as proteins contain several immunological determinants. This means that the antibody directed against the protigen is not always the same and directed only against skin in general. The protigen may be formed by some protein present in all of the skin, or may be derived from proteins producing organ-specific*antibodies.

IV. *The Antibodies are Produced in the Reticulo-Endothelial System, Lymph Nodes, Spleen. It is Postulated that the Lymphoid Tissue of the Skin may also Participate in the Process of Antibody Formation.*

The site of antibody formation in contact dermatitis has not been determined with certainty. The positive passive transfer of delayed-type sensitivity with lymphocytes from lymph nodes and spleen^{37,38,39,40,41} suggests that antibodies are produced in the lymphatic tissue.

If it is the lymphoid tissue which produces the antibodies, the assumption seems logical that the lymphoid tissue of the skin** might also carry out this function.

V. *The Antibodies in Contact Dermatitis are Directed Both Against the Hapten (i.e., the Simple Chemical) and the "Protigen" (i.e., the Specifically Altered Skin Protein).*

Mechanism of Antibody-Antigen Reaction in Delayed Type Sensitivity

As work with free antibodies in this type of sensitivity has not been feasible so far, we can only assume that these antibodies will behave in a similar fashion as those in anaphylactic sensitivity. Two main facts have to be considered—the antibody or antibodies produced by a conjugated antigen may react with different groups of the antigen (see also Table II, page 649); they may be directed against one or several of the following:

- A. The hapten only.
- The protein part (protigen) only.

*Species-specificity and organ-specificity are general terms; they do not imply that there is just one antibody or antigen responsible for either one. In species-specificity it is well known that sensitization to one member of a species may produce sensitization to other members of the same group (horse, donkey); but the antigens are not necessarily the same. This is shown by the fact that sensitivity is less pronounced to proteins of more distant members of the group; furthermore, hares' serum will produce antibodies both against rabbits and hares; but when injected into rabbits, it will produce antibodies to hare only and not to rabbits. Similar conditions exist in organ-specificity. Kidney substance may produce antibodies to lung tissue as well as to kidney tissue, but the antibodies are not identical. Therefore, we may expect in some instances of skin sensitivity, specific sensitivity to the skin or even to some specific part such as the follicular apparatus, the epidermis or dermis, in others combined sensitivity to several structures or perhaps even sensitivity to protein structures which are found also in other organs, e.g., the mucous membranes.

**The presence of preformed lymphoid tissue in the skin has been known for a long time.⁷⁷ That this tissue can be stimulated by allergic processes is indicated by the fact that the benign lymphocytoma of the skin often follows a dermatitis, or other allergic inflammatory processes.^{19,51} These lymphocytomas, in contrast to leukemic infiltrations, are characterized by the presence of the so-called "germ centers" which Hellman termed "reaction centers." Hellman and White⁴⁵ believe that these reaction centers have also the task of manufacturing antibodies.

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- B. Both the hapten plus protigen.
Independently.
Simultaneously.
- C. Some new antigenic entity.

From the experience with anaphylactic sensitivity, it is evident that a conjugated antigen usually engenders more than one sort of antibody. There is no reason why this should not occur in delayed type sensitivity. Haurowitz's³⁶ experiments definitely established the existence of antibodies which are directed simultaneously against hapten *and* protigen, a possibility which has also been suggested by the experiments of Heidelberger and Kendall,⁴³ and of K. Meyer.⁷⁰ That the antibody against conjugated antigens may be directed not only against the hapten, but also some adjacent parts of the protein, repeatedly has been pointed out by Landsteiner.

A dual action of the antibody in contact dermatitis, both with the hapten and the protein used in forming the protigen had been assumed by Rostenberg⁷⁸ in his theory about contact type sensitization. "Because of this protein specificity the antibody would attach to tissue containing this protein. It is further postulated that this attachment constitutes the state of being sensitized but that a reaction becomes manifest only when the allergen (probably as the simple chemical) comes along to complete the reaction." This theory is similar to the one proposed here; it recognizes the dual activity of the antibody for the production of a clinical reaction. However, in Rostenberg's theory, the protein-directed part of the antibody accounts only for the attachment to the shock tissue. If Rostenberg's assumption should prove correct that this attachment in contact dermatitis is connected with some 'protein-directed function of the antibody, that would not seem to be the whole function of the protigen-directed affinity of the antibody.* According to Rostenberg's theory, the essential requirement for the formation of conjugates is "that these conjugates be formed in an area rich in macrophages." Why such antibodies should attach themselves to various skin structures, that question is not answered. If, however, our assumption is correct that the conjugate is formed by a combination of the hapten with specific skin structures, then an elaboration of Rostenberg's theory would lead to the attachment of the antibodies to such structures and would explain the specific shock organ. A clinical reaction then might be elicited by action of the hapten only, or by a simultaneous action of hapten and protigen, or by the protigen alone or any combination of these. That the hapten alone is responsible for the elicitation of the eczematous response, as Rostenberg suggests, is possible, but not proven by the negative attempts to produce such reactions with conjugates. This could be decided only if it could be shown that natural conjugates (derived from the skin or lymphnodes) are capable of sensitizing by the intradermal route, but not able to elicit reactions in sensitized skin.

*There must be some way in which the antibody attaches itself to the shock tissue; this, however, is not a problem specific to delayed type sensitivity. It also pertains to immediate whealing sensitivity. Here the antibody may be attached to one or more organs, such as the mucous membranes of the eyes or nose (hay fever) or lungs (asthma), or skin (atopic dermatitis); nothing is known about the mechanism of this attachment, neither in anaphylactic-atopic sensitivity, nor in passive transfer of the Prausnitz-Küstner type, nor in contact dermatitis. But there are some differences between the atopic and delayed-type sensitivity. I shall mention only that the passive transfer of atopic reagins induces only localized sensitivity, whereas the cellular transfer of tuberculin-type sensitivity confers sensitivity to the whole skin.

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VI. Under Certain Circumstances, the Simple Chemical Which Usually Unites with a Protein to Form a Conjugate, May only Alter some Skin Protein or Proteins into Specific Antigens Without Combining with Them.

Such a possibility has been suggested by Ingram.⁴⁸ To my knowledge this mechanism has not been demonstrated as yet in contact dermatitis; some experiments of mine which seem to support this possibility will be published later. Sulzberger⁴⁹ suggested that alteration and liberation of skin constituents through infection, physical agents or reaction to allergens, may create and liberate skin antigens which in turn produce skin specific antibodies which when reacting with skin antigens available, produce reactions in the skin itself. It is now known that physical agents (e.g., ultraviolet rays),⁵⁰ as well as chemicals (e.g., staphylococcus toxin) may so alter body-own proteins that they become antigenic. That altered body-own proteins may become antigenic for the host is a well established fact. Normally body-own proteins cannot act as antigens in the individuals from which they are derived unless they have been altered and in this way become "foreign" to the organism.* However, although only altered body-own proteins may become antigenic for the species from which they are derived, the antibodies produced may also react with the unaltered, original proteins (Landsteiner,⁵¹ p. 42; Boyd⁶ p. 93).

SUMMARY AND CONCLUSIONS

A hypothesis about the antigen-antibody mechanism in contact dermatitis is presented. It is based on the following:

I. The actual antigen in contact dermatitis is a complex of a simple chemical (hapten) with a protein.

II. The protein part of the conjugated antigen in contact dermatitis is not just a more or less non-specific "carrier," but is a specific part of the complex antigen. It is termed "protigen" in this presentation.

III. The proteins which combine with the hapten to form a complex antigen in delayed type skin sensitivity are derived from the skin, i.e., epidermis, dermis or its appendages. The same hapten (simple chemical or polysaccharid) may form several conjugates by combining with different proteins.

IV. The antibodies are produced in the lymphatic tissues. It is postulated that the lymphoid tissue of the skin may also participate in the process of antibody formation.

V. A conjugate may provoke several antibodies. Some or all of the antibodies in contact dermatitis are directed both against the hapten (i.e. the simple chemical) and the "protigen" (i.e., the specifically altered skin protein).

VI. Under certain circumstances the simple chemical which usually unites with a protein to form the conjugate, may only alter some skin protein or proteins into specific antigens without combining with it (autosensitization).

*This is borne out by experimental studies with kidney, brain, lens, as well as with skin antigens (Hopkins and Burky,⁴⁷ Sulzberger, Hecht and Weil.⁴²).

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This theory may help to explain the following problems of contact sensitivity (pages 635 to 641) :

- 1) Contact sensitivity is usually confined to the skin, but does not affect the mucous membranes, and vice versa.
- 2) Different chemicals produce different patterns and pictures of contact dermatitis.
- 3) Follicular trichophytosis (kerion or sycosis barbae) produces follicular trichophytids, whereas the vesiculo-bullous dermatophytosis of the feet usually leads to a vesicular dermatophytid.
- 4) Certain aspects of localized sensitivity.
- 5) Certain inconsistencies in cross sensitivity.
- 6) The theory might clarify the relationship between contact dermatitis and autosensitization, especially in regard to certain allergids and erythroderma.

The immunological background of the hypothesis is reviewed in regard to forms of skin sensitivity (page 642), complex antigens (page 642), antibody formation (page 645), and autosensitization (page 647), and the supporting evidence for these postulates is presented (pages 648 to 654).

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For further references, the reader is referred especially to Haxthausen's review on "Allergy in diseases of the skin."^{74b}

CONNECTIVE TISSUE REACTIONS

Fundamental Reactions of Ground Substance

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In the previous review²¹ was presented the concept that allergic and other tissue reactions may be manifestations of reactions which take place in part in the ground substance of the mesenchyme, and proposed that the ultimate understanding of basic reactive mechanisms might be reached, in one way at least, by this shifting emphasis from cellular to extracellular reactions.

Since then progress in this field has not been as definitive as we might wish, but in general this concept appears to be still worthy of serious consideration. Furthermore, the concept has been somewhat strengthened by studies which indicate that the effects of hormones such as the ovarian and pituitary preparations are intimately related to ground substance reactions. For example Baker and Castor² report that percutaneous administration of adrenal steroids to rats not only causes a cessation of hair growth limited to the area of treatment, but also atrophy of the dermis in such an area. This atrophy was shown to be due to atrophy of collagen fibers accompanied by a reduction in the cellularity of the connective tissue. Elastic fibers were not affected. They found it necessary to administer for eighty days 0.1 cc daily of concentrated adrenocortical extract (1 cc equivalent to 1 mg of 11-dehydro-17-hydrocorticotesterone). It must be remembered that C-11 oxygenated steroids are known to inhibit the hyaluronidase spreading phenomenon in rabbits and in mice.^{22,23,24} The C-11 oxygenated steroids appear therefore to act directly on the ground substance as well as on epithelial cells. Somewhat more direct evidence for this is given by Schneebeil.³⁰ In this study he made spreads of the loose connective tissue of sensitized adrenalectomized mice which had been treated with adrenal cortical extract or cortisone. The spreads were air dried and stained with May-Grünwald-Giemsa. Four hours after hormone treatment the fibroblasts contained large acidophilic cytoplasmic inclusions of irregular size and shape and there were changes as well in the ground substance. These findings were found but infrequently in non-sensitized adrenalectomized or intact mice. More recently Cornman⁸ using tissue cultures of newborn mouse heart muscle showed that when desoxycorticosterone was added to the nutrient media the culture was damaged, the damage being significantly greater to the fibroblastic proliferation than to the mesothelial elements. When the acetate salt was used the damage was minimal, an effect not explained except for the suggestion that the acetate is less soluble and therefore less effective at a given salt to solute proportion. Finally, when cortisone (0.05-0.15 mg/ml) was added to the desoxycorticosterone containing fluid, there occurred accelerated and intensified damage. This seems to demonstrate a *direct* effect on fibroblasts, removed in tissue culture from the adrenal influence which the studies reviewed above indicate to be necessary. It also appears to be a promising method by which such direct effects of drugs and hormones on cells may be studied.

With regard to advances in our knowledge of the chemical nature of the

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ground substance, Meyer,²⁰ an outstanding contributor to this field, tells us that now five distinct mucopolysaccharides can be distinguished: 1. *Hyaluronic acid*, which is sulfate free and is rapidly digested by both testicular and pneumococcal hyaluronidase, 2. *Chondroitin sulfate A*, found only in hyaline cartilage and hydrolized only by testicular hyaluronidase, 3. *Chondroitin sulfate B*, which is resistant to both hyaluronidases, 4. *Chondroitin sulfate C*, differing from A only in optical rotation, and 5. *Hyaluronosulfate*, which has been obtained only from cornea. He summarizes the sources of mucopolysaccharides based on isolation in the following table⁸ (modified):

TABLE I.

Group	Tissue	Hyaluronic Acid	ChS-A	ChS-B	ChS-C
I	Vitreous Humor	+	—	—	—
	Synovial Fluid	+	—	—	—
	Mesothelioma	+	—	—	—
II	Hyaline Cartilage	—	+	—	+(?)
III	Heart Valves	—	—	+	+
	Tendon (pig and calf)	±	—	+	+
	Aorta	—	—	+	+
IV	Skin (pig and calf)	+	—	+	—
	Umbilical Cord	+	—	—	+

It might be added that human skin had been previously reported to contain hyaluronic acid and a sulfate ester which is probably one of the chondroitin sulfates.²⁵

These observations are of more than chemical importance. Questions raised necessarily include the reasons for the various distribution patterns, mechanisms of formation and the changes which may take place in the location and distribution of the various fractions under the influences of physiological and pathological stimuli.

For example, indirect evidence obtained by histological methods^{14,16,18} indicates that in various pathological conditions there is an accumulation of mucopolysaccharides in such tissues as the nodules of rheumatoid arthritis,¹ Aschoff bodies of rheumatic myocarditis,³ in disseminated lupus erythematosus¹⁵ and in the coxcomb on the application of sex hormones¹⁰ or pituitary hormones.¹⁷ In granulation tissue the metachromatically staining material greatly diminishes as the scar matures^{4,34} and it is presumed⁴ that hyaluronic acid is transformed during scar tissue formation into a substance which is no longer destroyed by the enzyme, and that it contributes to the formation of new fibrils which eventually form the adult scar. In human skin the formation of dense collagen fibers is accompanied by a reduction in the ratio of hyaluronic acid to chondroitin sulfate,³⁵ suggesting this to be an intermediate step in the formation of collagen fibers. This association of metachromatic substance with elastic fibers is noted in the case of small and large vessels.³ Furthermore, aging processes may involve qualitative differences in the types of mucopolysaccharides, as shown for the basement membrane of skin.¹³

Aside from such anatomical contributions there is some data pointing to important physiological functions of ground substance. Hyaluronic acid may be involved in water retention,¹⁹ and Meyer further suggests that the sulfated mucopolysaccharides may act as cation exchange resins. It has been shown that both *in vitro* and *in vivo* hyaluronidase depolymerizes synovial fluid²⁸ and that the synovial fluid of arthritic joints is highly de-

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polymerized.²⁹ In addition hyaluronidase produces a marked increase in Na and K in synovial fluid,³⁷ suggesting that these ions are liberated in the course of depolymerization and thus may initiate important ionic shifts. Finally, little is known of any protein complexes in the ground substance except that proteins are firmly bound to the sulfated mucopolysaccharides and that proteolytic enzymes are able to attack the ground substance even more effectively than hyaluronidase.⁹ It is probable that the ground substance should be thought of as a highly polymerized carbohydrate-protein complex.¹³

Furthermore, it seems to be generally accepted that the ground substance is in a highly plastic state of organization.⁵ In the case of bone, Cobb⁷ has suggested that the degree of aggregation increases in association with calcification, since the intensive staining reaction of young bone indicates the presence of many free reactive groups and therefore a low degree of polymerization. Older bone stains less intensely and therefore would be more highly polymerized. By giving parathyroid hormone to rats and studying bone and kidney sections in which the glycoproteins and other carbohydrate containing components were visualized with the periodic acid-leucofuchsin method, Engel¹¹ concluded that, directly or indirectly, parathyroid hormone depolymerizes the ground substance. This was accompanied by an increase in serum mucoproteins which sometimes reached a level five times that of the control animals. In this case it would appear that the hormonal influences on the ground substance of bone result in depolymerization, which in turn leads to liberation of muco-proteins which diffuse into the blood and probably carry with them bone salts.

Whether the depolymerization is affected directly by the hormone or by the liberation of depolymerizing enzymes is not clear at this time. The latter is more probable. That some of the breakdown of ground substance is engineered by enzymes has been suggested by several investigators.^{27,31,32,33,36} In any case, evidence is accumulating that hormones exert a powerful effect on the ground substance, as for example the effect of estrogen and relaxin.²⁶ Likewise, changes in the ovarian tissue which are apparently seen normally in the estrous cycle can be exaggerated by the administration of gonadotrophin.^{6,12}

We seem to be heading therefore in the direction of linking hormone effects more directly to changes in the ground substance. This is particularly interesting in view of the observed marked clinical and experimental effects on connective tissue which are produced by ACTH and cortisone. As a matter of fact, this reviewer ventures to predict that in the years to come the dramatic clinical effects of ACTH and cortisone will be overshadowed by the results of research they have stimulated on this fundamental concept of the ground substance, and there is reason to believe that research in this field will ultimately explain many of the general phenomena of cellular and tissue reactivity.

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ARE STUDENTS OF ALLERGY DECREASING?

When the American College of Allergists was incorporated in 1942, there were then in existence two national allergy societies whose combined membership represented about 250 physicians known to be applying allergy to their specialties. It was predicted by interested skeptics that there were not sufficient patients suffering from allergic diseases to warrant a new organization! The suggestion that there was need for 2000 allergists in the country was met with ridicule. At that time, journals of dermatology, pediatrics, gastroenterology, rhinology and internal medicine were publishing observations on hypersensitiveness encountered in their various specialties. It was evident that there was need for a liberal educational program which would interest young physicians in all these specialties to recognize the importance of allergy and apply it to their practices.

Instructional Courses were initiated by the College to arouse the interest of beginners in allergy, and as a refresher course for those already practicing allergy. From the onset, these courses met with increasing success. The question has arisen as to whether the number of allergy students is decreasing. However, there are three annual instructional courses in allergy by national allergy societies, as well as intensive courses by some of the medical schools. Annual meetings of the various specialties now include separate programs on allergic disease. The result has been that over 2000 physicians are now known to be applying allergy conscientiously to their practices.

Since the syndromes of allergic diseases are met in the practice of all specialties, the increasing interest and importance of recognizing these syndromes is evident. The College had 170 registrants for its Graduate Instructional Course at Pittsburgh last April, and based upon the number of applicants already for the meeting to be held in Chicago, April 24-29, 1953, there is every reason to believe that interest in allergy will never reach the saturation point.

COLLEGE INSTRUCTIONAL COURSE AND NINTH ANNUAL CONGRESS

The combined Graduate Instructional Course in Allergy and Ninth Annual Congress of The American College of Allergists, Inc., will be held at the Conrad Hilton (The Stevens), the largest hotel in the world, at Chicago, April 24-29, 1953.

The first three days, April 24, 25, 26 (Friday, Saturday and Sunday), will be devoted to an intensive graduate instructional course in the diagnosis and treatment of all phases of allergy. The chairman of the Instructional Course is Dr. Leon Unger, 185 Wabash Avenue, Chicago 1, Illinois, and the chairman of the Local Committee of Arrangements is Dr. Morris A. Kaplan, 116 South Michigan Avenue, Chicago 3, Illinois. Elaborate detailed arrangements are now being made by both chairmen for the instructional course and the congress, including entertainment, scientific and technical exhibits, et cetera. Ample registration service is being furnished, both for the Instructional Course and the Scientific meeting so that there will be no delay when registering.

INSTRUCTIONAL COURSE

Friday morning, April 24, will be devoted to fundamentals of allergy. Immunology, pathology, etiology, diagnosis and general treatment of allergies will be treated by experts. Friday afternoon will be devoted to bronchial asthma and allied chest conditions, including diagnosis, treatment and differential diagnosis.

Saturday morning, April 25, will be taken up with the subject of nasal allergy and all its factors. Saturday afternoon the instructors will present dermatologic allergy.

Sunday morning will be devoted entirely to pediatric allergy, and Sunday afternoon to drug allergy, allergic headache, gastrointestinal allergy, miscellaneous allergies and psychodynamics in adult allergy.

There will be five luncheons each day, Friday, Saturday, and Sunday, for five separate groups in different rooms, twenty-five allotted to each room. There will be a moderator and selected speakers for each luncheon. Registrants will be afforded the opportunity of having three choices of these luncheons which will embrace all phases of allergy.

COLLEGE INSTRUCTIONAL COURSE

On Friday night, from 8:00 to 8:40, there will be colored movies in connection with a bronchoscopic clinic showing the differential diagnosis of wheezing. From 8:40 to 10:00, there will be five speakers who will be given fifteen minutes each for a round table on respiratory, dermatologic, pediatric, and food allergy. On Saturday night there will be an illustrated lecture on collagen diseases followed by round tables on ACTH and cortisone.

There will be one hour devoted at the end of each afternoon to demonstrations on office procedures, making of extracts, skin testing, et cetera. The committee on psychosomatic allergy has planned an extensive program for Sunday evening consisting of four clinical seminars.

SCIENTIFIC PROGRAM

The scientific session will take place April 27, 28, 29 (Monday, Tuesday and Wednesday). Dr. Giles A. Koelsche has appointed chairmen of the various sections: dermatology, pediatrics, psychosomatics, otolaryngology, and general. All those interested in presenting papers before any of these sections should write to Dr. Giles A. Koelsche, Over-All Chairman of the Program Committee, Mayo Clinic, Rochester, Minnesota, indicating their preference, and giving the title of their paper, as well as sending an abstract of not more than 750 words in triplicate. The deadline for papers is December 1, 1952.

Monday, April 27, will be devoted entirely to the general section. The dermatologic and psychosomatic sections will meet Monday evening from 7:00 to 10:00 p.m.

Tuesday morning, April 28, the president, Dr. J. Warrick Thomas, Richmond, Virginia, will address the Congress from 9:00 to 9:20. Following the president's address, Dr. Larry L. Halpin of Cedar Rapids, Iowa, will introduce the incoming president, Dr. M. Murray Peshkin, New York City, and the guest speaker, Dr. C. M. Pomerat, Professor of Cytology, University of Texas, Medical Branch, Galveston, Texas. He will present an illustrated lecture with colored moving pictures on "Direct Observations on Human Allergic Cells with Tissue Culture Technique." From 10:00-10:30 there will be a recess to visit the exhibits and at 10:30 there will be a Business Meeting at which all Fellows, both Active and Associate, are urged to be present.

There will be two round-table luncheons on Tuesday held at 12:30 to 2:00 on otolaryngologic and pediatric allergy. In

COLLEGE INSTRUCTIONAL COURSE

the afternoon, from 2:00 to 5:30, there will be papers presented before the pediatric and otolaryngologic sections.

Tuesday evening there will be a cocktail hour sponsored by the Schering Corporation, Bloomfield, New Jersey, followed by a banquet at 8:00 o'clock and an elaborate program of entertainment. Wine will be furnished through the courtesy of the Nepera Chemical Company, Yonkers, New York.

Wednesday morning, April 29, the section on psychosomatic allergy will present an extensive program followed by discussions. It was decided that this section would end at 1:00 o'clock to allow more time to be spent with the technical exhibitors and ample time to prepare for departure.

Social activities and a program of entertainment is being arranged for the ladies by Mrs. Leon Unger and Mrs. Morris Kaplan. They are arranging a Hostess Committee composed of physicians' wives to aid in planning this entertainment. There will be teas, luncheon at the Kungsholm, a style show, a TV show, and a sight-seeing tour to the Adler Planetarium, the Art Institute, and places of interest for which Chicago is famous. Provision will be made by a Travel Bureau to make all changes in travel reservations, and for the sale of theatre tickets, matinees, current concerts, or other entertainment. You'll find the Ladies' Headquarters an ideal place to meet old friends and make new ones.

The program as announced is tentative and subject to change. The final program will appear in the January-February issue of the *ANNALS OF ALLERGY*, and a complete program booklet will be furnished to only those at the meeting.

All members will be receiving a hotel reservation card giving the room rates and other information required by the hotel management. *All reservations must be made directly with the hotel* on this card which will be sent you by March 1. It is necessary for you to state exactly the time of your arrival, time of departure, and type of accommodations you desire.

For any detailed information, address the Secretary-Treasurer, The American College of Allergists, Inc., 401 LaSalle Medical Building, Minneapolis 2, Minnesota.

The price of the Instructional Course will be \$50.00 including three round table luncheons. All checks should be made payable to The American College of Allergists.

News Items

FIFTH INTERNATIONAL CONGRESS OF OTO-, RHINO-, LARYNGO-, BRONCHO- AND ESOPHAGOGY

The International Committee for the International Congress of Otolaryngology has invited the Dutch Society to organize the Fifth International Congress in the Netherlands. The Congress will be held June 8-15, 1953, in Amsterdam. President of the Congress Committee is Professor E. Huizinga, Amsterdam. Secretary-General is Dr. W. H. Struben (J. J. Viottastratt 1, Amsterdam-Z.). One of the main subjects is Allergy. G. Dohlman (Lund) will review the "Theory of Allergy," F. H. Hansel (St. Louis, Mo.) the "Methods of Allergic Examination," and R. Melchoir (Paris) the subject of "Non Allergic Hypersensitivities." P. Kallós (Helsingborg) will open the discussion on allergy.

BUENOS AIRES INSTRUCTIONAL COURSE IN ALLERGY

The Minister of Education announces that the National University of Buenos Aires faculty of Clinical Medicine will conduct a course on allergic diseases under the direction of Dr. Leopoldo Herraiz Ballesterio, F.A.C.A., at the Hospital Rivadavia, from September 1 to October 30, Monday, Wednesday and Friday, from 11:00 to 12:00 o'clock. During this time there will be twenty-nine conferences covering the fundamentals, differential diagnosis and treatment of allergic diseases involving all the domains of the body, both in adults and children.

CHILEAN SOCIETY OF ALLERGY

The Chilean Society of Allergy has just elected a new Board of Directors which is as follows:

President—Z. Bernáth, M.D.

Vice President—A. Estevez, M.D.

Secretary-Treasurer—H. Richetti, M.D.

The Chilean Society of Allergy is a member of the International Association of Allergology.

AMERICAN ACADEMY OF PEDIATRICS

For the forthcoming American Academy of Pediatrics 21st Annual Meeting, to be held in Chicago, Illinois, in the Palmer House from October 18 to 23, the following allergy facets will be discussed:

Seminar on Pediatric Allergy, JEROME GLASER.

Round-table Discussion on Pediatric Allergy, JAMES C. OVERALL.

Symposium—Basic Mechanisms in Allergic Diseases

Chairman: BRET RATNER, M.D., New York City

1. Antigen-Antibody Mechanism in Allergy and the Mechanism of Antibody Formation
T. N. HARRIS, M.D., Children's Hospital, University of Pennsylvania, Philadelphia, Pa.
2. Physiological Mechanisms of Anaphylaxis and Allergy
BRET RATNER, M.D., New York City
3. Pathology of the Allergic and Collagen Diseases
MILTON G. BOHRD, M.D., Rochester, New York
4. THE MECHANISMS OF ALLERGY TO DRUGS AND ANTIBIOTICS
A. ROSTENBERG, Jr., M.D., Chicago, Illinois

NEWS ITEMS

POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Fifth Annual Postgraduate Course on the Recent Advances in Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education and the New York State Chapter of the American College of Chest Physicians, will be presented at the Hotel New Yorker, New York City, November 10-14, 1952.

This course is open to all physicians, but the registration will be limited. Tuition fee is \$50.00; applications will be accepted in the order in which they are received.

A copy of the prospectus together with an application form can be secured from the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

This course has been approved for credits by the American Academy of General Practitioners.

NEW JERSEY ALLERGY SOCIETY

At the last meeting of the New Jersey Allergy Society the following officers were elected: President, Dr. William Greifinger of Newark, Vice President, Dr. Edward Seidmon of Plainfield, Secretary, Dr. William Nevius of East Orange, Treasurer, Dr. Joseph Skwirsky of Newark.

The Executive Committee consists of Dr. Roselyn Barhash of Teaneck, Dr. Frank Rosen of Newark, Dr. Harry Hershey of Jersey City, and Dr. Frank H. Feldman of Newark.

On October 16, 1952, the New Jersey Allergy Society is having a meeting combined with the stated meeting of the Academy of Medicine of Northern New Jersey. Dr. Leo H. Crip, Assistant Professor of Medicine of Pittsburgh School of Medicine, and Area Consultant to Veterans Administration, will be the guest speaker. The topic, "The Management of the Allergic Child."

THE HOXSEY TREATMENT FOR CANCER

It should be of interest to all physicians to learn the facts at hand concerning the Hoxsey drugs for the treatment of cancer. The following information has been furnished by the Food and Drug Administration, Washington, D. C.

The U. S. Court of Appeals for the Fifth Circuit in the case of U. S. v. Hoxsey Cancer Clinic, a Partnership, and Harry M. Hoxsey, an Individual, after a vigorously contested case tried in the U. S. District Court at Dallas, Texas, handed down an opinion which reverses the judgment of the trial judge (William H. Atwell, Northern District of Texas) and directs that Court to issue an injunction prohibiting the defendants from distributing in interstate commerce brownish-black and pink liquids intended for the treatment of cancer in man.

The letter from the Commissioner of Food and Drugs states further:

"In many parts of the country, people are taking the Hoxsey medicines in the belief that they may be an effective treatment for cancer. Friends and relatives of cancer victims frequently query local physicians concerning this treatment. You may wish to publish information about this case so that physicians will have the facts at hand concerning these drugs, in the event of such inquiries.

"The following important principles are laid down in the Circuit Court opinion, based on testimony by cancer experts.

1. "****there is only one reliable and accurate means of determining whether what is thought to be cancer is, in truth and fact, actually cancer. This requires a biopsy, a microscopic examination of a piece of tissue removed from the infected and diseased region."

2. "****the opinion of a layman as to whether he has, or had, cancer, or a like opinion as to whether he has been cured and no longer bears the disease, if, in fact, it ever actually existed, is entitled to little, if any, weight."

3. "****despite the vast and continuous research which has been conducted into the cause of, and possible cure for, cancer the aggregate of medical experience

NEWS ITEMS

and qualified experts recognize in the treatment of internal cancer only the methods of surgery, x-ray, radium and some of the radioactive by-products of atomic bomb production.

4. ***Upon such subjects a Court should not be so blind and deaf as to fail to see, hear and understand the import and effect of such matters of general public knowledge and acceptance, especially where they are established by the overwhelming weight of disinterested testimony***.

"The Hoxsey Clinic is located in Dallas, Texas, and ships its drugs to patients in many other states. According to the unanimous opinion of the Court of Appeals, consisting of Judges Russell, Hutcheson, and Rives, 'the overwhelming weight of the credible evidence requires a conclusion that the representation that the Hoxsey liquid medicines are efficacious in the cure of cancer is *** false and misleading. The evidence as a whole does not support the finding of the trial Court that "some it cures, and some it does not cure, and some it relieves somewhat."'"

To anyone interested background information on the Hoxsey Clinic will be furnished in a report prepared by the Division of Medicine of the Food and Drug Administration.

RESEARCH GRANTS

Research grants by the Swedish Royal Medical Board have been awarded to Dr. Sv. Hellerström and associates (Stockholm) for investigations on turpentine sensitization and to Dr. P. Kallós and associates (Helsingborg) for continued work on baker's asthma.

MEDICAL AUTHOR WRITES FOR LAY READERS

The August, 1952 number of *Scientific American* (Vol. 187, No. 2) contains a very informative article on "Asthma," for non-medical readers, by Dr. William Kaufman, F.A.C.A., of Bridgeport, Connecticut. The article contains two excellent figures.

Dr. Kaufman is Chairman of the Public Education Committee, a member of the Rheumatism and Arthritis Committee, and a member of the Psychosomatic Committee of the College. He is well qualified to present the pathophysiological mechanisms of allergic diseases which are often influenced by psychological mechanisms.

SECTION ON ALLERGY

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND ACADEMY OF MEDICINE OF BROOKLYN

At the last meeting of the Section on Allergy of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn, the following officers were elected:

President—Emanuel Schwartz, M.D.

Vice President—Harry Markow, M.D.

Secretary—Harry Leibowitz, M.D.

Treasurer—Solomon Slepian, M.D.

Elected as Honorary Members were: Albert F. R. Andresen, M.D., and Bela Schick, M.D.

PROCEEDINGS OF THE SECOND NATIONAL AIR POLLUTION SYMPOSIUM

The Stanford Research Institute, Stanford, California, now has available the Proceedings of the Second National Air Pollution Symposium, held May 5 and 6, 1952, at Pasadena, California. This symposium was sponsored by Stanford Research Institute in co-operation with California Institute of Technology, the University of

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California and the University of Southern California. It contains 144 pages, illustrated, including twenty pages by selected experts on the various phases of air pollution.

* * *

Dr. B. G. Efron, F.A.C.A., has inaugurated a new service in allergenic extracts at 7 Gull Street, New Orleans, La. Dr. Efron was one of the pioneers in this country to develop a better quality of allergenic extracts which would be available to the practitioner, which, in turn, would improve the quality of therapy when managing the allergic patient.

To meet this problem, a group of allergists some years ago joined in support of a project to develop techniques for preparing extracts of all the generally known allergens with the same high degree of purification and standardization that had previously been attained only in house-dust extracts (by the Boatner-Efron process). Because of his contributions to the study of house-dust, Dr. Efron was chosen to carry on this work.

The allergenic extracts subsequently perfected and the resultant service rendered to this limited group of participating allergists proved so rewarding that it has now been decided to offer such service to the profession at large.

These highly purified extracts are now available. The same concentrate may be used diagnostically as well as therapeutically.

* * *

In the September 15, 1952, issue of *Life*, there is a pictorial story featuring **Dr. Dorothy Baruch** (Mrs. Hyman Miller) of Beverly Hills, California, who wrote a book about play therapy called "One Little Boy." This book was reviewed in the July-August issue of the *ANNALS OF ALLERGY*. The article illustrates two children, one a boy and one a girl, and the methods used by the psychiatrist to help them relieve themselves of their frustrations.

* * *

As the *ANNALS* goes to press, we announce with deep regret the sudden death of Dr. Emmanuel B. Schoenbach, Editor-in-Chief of the *Quarterly Review of Internal Medicine*, which is published by the Washington Institute of Medicine, and is widely read.

DEFINITIONS

(Continued from Page 632)

positive skin tests might parallel clinical food sensitivity. Occasional patients with inhalant sensitivities fail to give skin test reactions, although they respond clinically to inhalation of pollens and pollen extracts.

To those tidy minds that yearn to see the terminology of our enormously complicated and far-reaching specialty "squared away," we would counsel a patient restraint and a careful use of the technical terms at our disposal, as well as the new ones, in accordance with the solidly based advances in our exciting special science.

For those who may respect the wisdom of the past, we would recall Samuel Johnson's remark, "definitions are hazardous," and the more vigorous conclusion of Disraeli—"I hate definitions!"

BOOK REVIEWS

A TEXTBOOK OF PHARMACOLOGY. Principles and Application of Pharmacology to the Practice of Medicine. By William T. Salter, M.D., Professor of Pharmacology, Yale University School of Medicine. 1240 pages, 284 figures. Price \$15. Philadelphia: W. B. Saunders Company, 1952.

This compact yet comprehensive illustrated textbook covers the entire field of our knowledge of modern pharmacology to date. The numerous figures illustrating the physiological action of drugs are excellent. The book records the personal experiences of an international authority and reflects the choices of one who has spent many hours at the bedside of clinical patients as well as long nights in the laboratory. Throughout the book it is apparent that the author has first in mind the course of human disease and the hope that it may be ameliorated. It is difficult to separate the rapid accumulation of fundamental facts and theory in pharmacology. The author, who has been a teacher for many years, selects those things which he believes a medical student and up-to-date practitioner should understand and presents it in a scientific and dynamic manner. The fundamental statements are selected from material which has a clinical bearing. He construes medical pharmacology in terms of pathologic physiology, assuming that disease has a rational and mechanistic explanation in most instances.

There are four parts divided into nine sections dealing with the general principles of pharmacology, drug action on physiological mechanisms, application of drugs to clinical medicine, and toxicology. The chapters on the antihistamines, the adrenal cortex, and sodium and potassium metabolism are excellent. The chapter on peripheral autonomic blocking agents as well as the application of drugs to body systems should receive special mention. Medicaments used in the treatment of dermatoses could perhaps be more comprehensive. Section 8 on toxic substances of industrial and homely origin, in view of our increasing interest in common industrial poisons and air pollution, is very timely. Antiseptics and germicides are presented in detail. There are references at the end of each chapter, and the index is more complete than that in most books on pharmacology.

DE RE MEDICA, Third Edition. 643 pages, 46 color plates, numerous tables and charts. Indianapolis: Eli Lilly & Company, 1951.

This third edition published by Eli Lilly & Company emulates the purpose and title of the original classic work of Celsus, *De Re Medica*, the earliest treatise for medical reference, first published in Florence in 1478. The book is a fair and impartial presentation of up-to-date knowledge of diseases together with very practical discussion of symptomatic treatment as well as specific measures.

Section 1 includes the infectious, systemic, and allergic diseases of the cardiovascular system, blood and bone marrow, respiratory system, alimentary tract, nervous system, endocrine glands, male and female genital systems, skin, nutrition, diseases due to physical and toxic agents, and unclassified diseases. Section 2 deals with the action and uses of drugs with figures and structural formulas, biological therapy, water salts and osmotic agents, action and use of drugs used with diseases of the cardiovascular system and the other systems of the body previously mentioned. There is an excellent article on the action and use of endocrine preparations, insulin, antithyroid drugs, estrogens, pituitary extracts, ACTH and cortisone, the antihistaminic drugs, and miscellaneous drugs. Section 3 contains remarkable color plates which give the impression of being three-dimensional. There are nineteen atomic charts, eight plates of skin lesions commonly misdiagnosed, thirteen plates

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on the blood in health and disease, one on the flocculation tests for the serodiagnosis of syphilis, and a number of test charts. Section 4 deals with laboratory tests as done in the modern hospital laboratories today.

It is disappointing that with the growing importance of allergic diseases the tests for the study of the cytology of the nasal secretions, particularly with reference to the content of the eosinophils of the nasal secretions and the detailed procedures for making the eosinophil counts in the blood as well as the Thorn test, are so frequently omitted in books of this kind.

Sections 5 and 6 deal with poisons and antidotes, Latin words, weights and measures, equivalents, food values, diets, and many other useful tables. Section 7 presents a selected list of Lilly products. The index is thorough. Compilation of data of this kind entails much labor, and the publishers are to be congratulated for making available such a book to selected members of the medical profession. The binding is a durable, flexible one for use in the laboratory.

DIABETES MELLITUS. Principles and Treatment. By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. 289 pages, 31 figures, 40 tables. Price \$5.75. Philadelphia: W. B. Saunders Company, 1951.

With the campaign on for early detection of diabetes in the total populace, this book furnishes one of the most modern references extant on the subject. All non-essentials are omitted, and the book aims at instructing the student and the physician in the treatment of diabetes. Diabetes is probably one of the worst treated of all diseases compared to the knowledge of the means of its control. Tragedies are caused not only by ignorance and carelessness of patients but also by errors of physicians.

This volume correlates up-to-date principles in the understanding of diabetes and provides a practicable and simplified outline of therapy. Important concepts are repeated for emphasis, and illustrations lend considerable aid. It is estimated that there are nearly two million diabetic patients in this country. Our responsibilities embrace the early detection of the disease, adequate treatment, a continuous educational program, encouragement of research, and prompt clinical application of every advance achieved. Doctor Duncan's book is a challenge to the medical profession.

PHARMACOLOGY IN CLINICAL PRACTICE. By Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry; and Consulting Physician, Milwaukee County General Hospital and Columbia Hospital, Milwaukee, Wisconsin. 839 pages, 152 figures. Price \$12.50. Philadelphia: W. B. Saunders Company, 1952.

The text of this profusely illustrated volume is individualistic, and presents the kind of pharmacology which the author has taught for many years. The author is well known for his various editions of his "Treatment in General Practice." With his previous excellent clinical training the author, throughout the text, has tried to get away from pedagogical methods and to deal with the entire subject in a practical, rational manner which would help the physician in the proper treatment of his patients. The book considers specific diseases and the practical application by the pharmacologist in terms of symptoms instead of anatomical groups or organs or chemical grouping of drugs. The subjects of historical development of compounds, or the relationship of chemical composition and biologic activity, although very important subjects, are only of interest to the pharmacologist and graduate student of the subject and not to the undergraduate dental students or general practitioners.

The book contains two sections. One presents the pharmacological aspects of practically all of the important problems that arise in general practice and dentistry. Section II presents a few chemical and physical facts about the drugs discussed in